ejpmr, 2024, 11(7), 93-111

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

THERAPEUTIC STRATEGIES FOR COVID-19: A REVIEW OF CURRENT RESEARCH AND CLINICAL TRIALS

Apollos Ebi-erefa[1], Hyellavala Joseph Fomnya[2]*, Blessing Benjamin Awu[3], Garleya Bilbonga[4] and Inalegwu Adonyikwu[1]

[1]Department of Diagnostic Services, National Veterinary Research Institute, Vom, Nigeria.
[2]Department of Public Health, Faculty of Health Sciences, National Open University of Nigeria.
[3]Departmen of Nursing Science, Adamawa State College of Nursing and Midwifery, Yola, Nigeria.
[4]Department of Animal Production and Health, Faculty of Agriculture and Life Sciences, Federal University Wukari, Nigeria.

***Corresponding Author: Hyellavala Joseph Fomnya**

Department of Public Health, Faculty of Health Sciences, National Open University of Nigeria.

Article Received on 14/05/2024 **Article Revised on 04/06/2024** **Article Accepted on 24/06/2024**

ABSTRACT

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has prompted global health emergencies and a swift response from the scientific community. This review summarizes the current state of knowledge on the mechanisms of action and efficacy of several key drugs, including hydroxychloroquine, azithromycin, remdesivir, umifenovir, and others. The study highlights the potential benefits and limitations of these treatments, including their effects on viral replication, inflammation, and immune response. Additionally, it discusses the role of corticosteroids and convalescent plasma in managing severe cases of COVID-19. Epidemiological data reveal the rapid spread and significant morbidity and mortality associated with COVID-19. The virus primarily targets the respiratory system, but its impact extends to multiple organ systems, leading to diverse clinical manifestations. Research highlights the critical need for effective antiviral therapies and vaccines to combat the pandemic. Continuous surveillance, comprehensive clinical studies, and the development of robust healthcare strategies are essential to mitigate the virus's impact. This review emphasizes the urgent need for global collaboration in research and healthcare to manage and eventually overcome COVID-19.

KEYWORDS: COVID-19, Antiviral therapy, Immune response, Convalescence plasma.

INTRODUCTION

Towards the end of December 2019, an outbreak of an unknown cause of pneumonia characterized by fever, dry cough, fatigue, and occasional gastrointestinal symptoms was noticed in people who patronized a seafood wholesale wet market, the Huanan Seafood Wholesale Market, in Wuhan, Hubei, China (Huang et al., 2020). Within the initial fifty days of the outbreak, the novel coronavirus resulted in over 1,800 fatalities and infected more than 70,000 people. Chinese researchers identified this new virus as the 2019 novel coronavirus (2019-nCoV). On February 11, 2020, the World Health Organization (WHO) officially designated the illness caused by 2019-nCoV as coronavirus disease 2019 (COVID-19. The International Committee on Taxonomy of Viruses (ICTV) named the virus SARS-CoV2 and the disease COVID-19 (Cui et al., 2018; Lai et al., 2020). On March 11, 2020, The WHO classified COVID-19 as a pandemic. The disease has reached nearly every country. (Xu et al., 2020).

Severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) is the aetiology of coronavirus disease 2019 (COVID-19), an infection that manifests as flu-like symptoms, progressing in some cases to acute respiratory distress syndrome (ARDS) or myocarditis. (Yang et al., 2020; Zeng et al., 2020; Ruan et al., 2020; Zheng et al., 2020). COVID-19 has a mean incubation period of 5.2 days (95% confidence interval, 4.1–7.0) (Li et al., 2020). Guan et al. (2020a) documented 1,099 cases of 2019-nCoV infection, identifying fever (87.9%) and cough (67.7%) as the predominant symptoms, while diarrhoea (3.7%) and vomiting (5.0%) were infrequent. Chest CT scans revealed abnormalities in 96% of SARS-CoV-2 patients, and 82.1% exhibited lymphopenia. The disease can deteriorate to severe disease with difficulty in breathing and severe chest symptoms corresponding to pneumonia in approximately 75% of patients ((Guan et al., 2020). SARs-CoV-2 infected individuals whose cases were fatal later developed acute respiratory distress syndrome which worsened within a short time and died of multiple organ failure (Huang et al., 2020; Chen et al.,

2020). Investigation of already existing drugs for new therapeutic purposes, especially to manage COVID-19 is key in fighting SARS-CoV-2 and other challenging emerging and reemerging diseases is of paramount importance (Fomnya et al., 2022)

MEDICATIONS USED DURING CLINICAL INTERVENTION OF COVID-19

Chloroquine (CQ) and its derivative, hydroxychloroquine (HCQ): Chloroquine (CQ) and its derivative, hydroxychloroquine (HCQ), are considered prophylactic drugs against malaria and as treatments for autoimmune diseases (Hu et al., 2020). Chloroquine alters the glycosylation of ACE2, which decreases the affinity of ACE2 for the coronavirus spike protein, reducing SARS-CoV-2 entry in vitro (Vincent et al., 2005). Chloroquine was found to inhibit SARS-CoV-1 infection and the sequence and structure homologies between SARSCoV-1 and SARS-CoV-2 suggest that chloroquine could reduce SARS-CoV-2 infectivity (Vincent et al., 2005). Additionally, chloroquine and hydroxychloroquine inhibit the Toll-like receptor (TLR) pathway; the TLR pathway is involved in pro-inflammatory cytokine signaling. Indeed, one in vitro study demonstrated that chloroquine inhibits SARS-CoV-2 entry (Wang et al., 2020a). The Guangdong province advised that individuals diagnosed with COVID-19, who do not have contraindications to chloroquine, should take 500 mg of chloroquine twice daily for 10 days (Zhonghua et al., 2020).

Remdesivir: Remdesivir is a prodrug that is metabolized into an adenosine nucleotide analog. It has demonstrated in vitro efficacy against SARS-CoV-2 (Wang et al., 2020a). Recently, it was observed that remdesivir has antiviral effects against several RNA viruses (including SARS/MERS-COV-2) infection in primate models other than humans, in cultured cells as well as in mice (Wang et al., 2020b). Remdesivir only and in combination with chloroquine or interferon beta significantly blocked the SARSCoV-2 replication and patients were declared as clinically recovered (Holshue et al., 2020; Wang et al., 2020).

Nitazoxanide: In vitro studies suggest that nitazoxanide shows anti-COVID19 and immunomodulatory activities (Lai et al., 2020). Nitazoxanide is a broad-spectrum antiviral agent undergoing clinical development for the treatment of influenza and other viral respiratory infections (Rossignol, 2016). As it is used extensively in clinical trials, nitazoxanide may be tested as a treatment against SARS-COV-2 (Rossignol., 2014).

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide): Favipiravir is an antiviral agent that selectively and strongly inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. Its antiviral efficacy diminishes in the presence of purine bases, suggesting it competes with purine nucleosides rather than pyrimidine nucleosides. Therefore, favipiravir with these unique profiles will be a promising therapeutic agent for RNA viruses (Furuta et al., 2017). Favipiravir may possess antiviral effects against the novel coronavirus, given that it belongs to the same category of single-stranded RNA viruses as the common influenza virus. However, its clinical use for treating COVID-19 is currently under evaluation to establish definitive evidence of its efficacy and safety (IATR, 2021).

Ivermectin: Ivermectin is an FDA-approved broad-spectrum antiparasitic agent that has recently demonstrated antiviral activity against a wide variety of viruses in vitro. In vitro, ivermectin has antiviral effects against several distinct positive-sense single-strand RNA viruses, including SARS-CoV-2 (Wulan et al., 2015). A statement was issued by the manufacturer of the drug saying that there is no tangible evidence ivermectin is effective against SARs-CoV-2 and that attempting such use may be unsafe (David, 2021). Nevertheless, because of the increase in cases and death counts, ivermectin use in Central and Eastern Europe, Latin America, and South Africa increased (Heidary et al., 2020).

Convalescent plasma transfusion therapy: Convalescent plasma consists of pooled plasma or immunoglobulins derived from patients who have recovered from an infection. In ten patients seropositive for SARS-CoV-2 and hypoxic, but not intubated, one dose of 200 ml of convalescent plasma led to a nearly immediately undetectable viral load and improved oxygenation in 3 days (Duan et al., 2020). Transfusion of 200–250 ml of convalescent plasma (on days 10 and 22) in five patients who were intubated with radiographic evidence of acute lung injury led to reduced hypoxia in all five and three were able to be weaned from mechanical ventilation (Shen et al., 2020a). The use of convalescent plasma was recommended before as an important treatment during outbreaks of Ebola virus, Middle East respiratory syndrome coronavirus, SARS-COV-1, H5N1 avian influenza, and H1N1 influenza (Hung et al., 2011; Zhou et al., 2007).

Corticosteroids: Corticosteroids have anti-inflammatory functions, and they can suppress inflammation during COVID-19-associated acute respiratory distress syndrome. Short-term (3-5 days) and very low doses (methylprednisolone 1-2 mg/kg/day) are recommended (Lai et al., 2020).

Azithromycin: A prospective trial in France of 22 patients noted that a combination of 600 mg hydroxychloroquine and azithromycin (500 mg on the first day and then 250 mg each day for the next 4 days) reduced viral load more effectively than hydroxychloroquine alone (Gautret et al., 2020a).

MECHANISMS OF THERAPEUTIC ACTION OF THE DRUGS OF CHOICE IN THE TREATMENT OF COVID-19

Mechanism of Action of Chloroquine (CQ) and Hydroxychloroquine (HCQ)

Mechanisms of CQ/HCQ as an Anti-viral drug: Chloroquine (CQ) and hydroxychloroquine (HCQ) may inhibit viral entry by serving as inhibitors of sialic acid biosynthesis, which are crucial for virus-cell ligand recognition. The in-vitro action of CQ against coronaviruses has been credited to the inhibition of the N-glycosylation of the cell surface viral receptor, the angiotensin-converting enzyme 2 (ACE2) for SARS-Cov-2, and possibly viral spike (S) proteins and in turn resulting in reduced binding affinity between cellular ACE2 and viral S protein (Vincent et al., 2005). CQ/HCQ may have inhibitory effects on virus cleavage and entry into the host cell which could result in blocking the viruses in endocytic vesicles (Quiros Roldan et al., 2020). CQ/HCQ could interfere with viral protein maturation processes taking place in the endoplasmic reticulum (ER)-Golgi intermediate compartment (ERGIC) and trans-Golgi network (TGN) vesicles which requires a low pH (Fehr and Perlman, 2015).

CQ/HCQ could also prevent virion budding, taking place when encapsulated viral genomes bud into the ERGIC membranes in which viral enveloped proteins are inserted, producing mature virions (Schoeman and Fielding, 2019). In infected airway epithelium, respiratory viruses activate the mitogen-activated protein kinase (MAPK) pathways, notably the p38 MAPK pathway, by binding to Toll-like receptors (TLRs). CQ has been shown to hinder viral infections through the prevention of p38 MAPK activation (Yang et al., 2016).

Mechanisms of CQ/HCQ as Anti-inflammatory drugs: CQ/HCQ are used as anti-inflammatory and immune-modulatory drugs in autoimmune diseases. These characteristics are derived from their several effects on the immune system cells and their regulation of important proinflammatory cytokines (Plantone and Koudriavtseva, 2018). Chloroquine (CQ) and hydroxychloroquine (HCQ) may disrupt the normal maturation and antigen recognition process of viral antigens by antigen-presenting cells (APCs), which depend on endosomal acidification for effective antigen processing. Through the process of phagocytosis, CME, caveolin-mediated endocytosis, and macropinocytosis, macrophages internalize pathogens, process their proteins, and present antigens to T cells (Guerriero, 2018).

Chloroquine (CQ) and hydroxychloroquine (HCQ) also alkalinize vesicles within the endosome-lysosome-autophagy pathway, potentially exacerbating interference with antigen presentation by antigen-presenting cells (APCs). This dual effect hampers both antigen breakdown and processing of major histocompatibility complex (MHC) molecules. Consequently, inhibition of antigen presentation diminishes T and B cell activation and differentiation, while also reducing the production of pro-inflammatory cytokines. The drug inhibits Ca^{2+} signaling and downstream events, involved in T and B cell receptor engagement with antigen, reducing their activation (Roldan et al., 2020). Further, CQ/HCQ hinders the differentiation and proliferation of T helper (Th) 17 cells, a subpopulation of CD4+ T cells characterized by the production of the pro-inflammatory cytokine interleukin-17 (IL-17) and is also associated with the pathogenesis of many inflammatory diseases such as RA and SLE (Yang et al., 2018).

Mechanisms of CQ and HCQ as anti-thrombotic: CQ/HCQ may act by interfering with platelet aggregation, reducing the activation of collagen and alpha granule release. HCQ has been shown to decrease ADP effects on platelets (Roldan et al., 2020). Besides their proper anti-thrombotic characteristics, CO/HCQ has shown the potential to inhibit NETs, successfully further reducing hypercoagulability (Boone et al., 2018). In vitro experiments on human umbilical veinous endothelial cells (HUVEC) have shown the protective effect of HCQ, which acts to revive the AnxA5 anticoagulant shield and consequently prevents the start of a coagulation cascade (Jacob et al., 2010). The capacity of hydroxychloroquine (HCQ) to reduce endothelial dysfunction has been investigated in animal models. HCQ improved endothelium-dependent dilatation by the amelioration of NO bioavailability and by the reduction of oxidative stress (Urbanski et al., 2018). HCQ affirmed its anti-thrombotic activity by reducing clot formation, ameliorating TGT, and improving endothelial relaxation. Additionally, HCQ ameliorated eNOS activation, improving the p-eNOS/eNOS ratio with consequent improvement of nitric oxide (NO) production (Miranda et al., 2019).

Modulation of Iron Metabolism: CQ/HCQ has been shown to regulate iron metabolism, impairing its homeostasis at various levels (Muriuki and Atkinson, 2018). CQ/HCQ treatment could result in the inhibition of Tf/TFR1 complex absorption and cellular iron starvation thereby inhibiting SARS-Cov-2 replication within the cell (Roldan et al., 2020). Iron starvation conditions induced by chloroquine (CQ) and hydroxychloroquine (HCQ) play a significant role in affecting immune cells involved in both innate and adaptive immune responses against the virus. Like all cells within the body, immune cells require iron for their actual functions and for their activation and growth (Porto et al., 2019). The Mechanism of Action of Chloroquine and Hydroxychloroquine as anti-viral, anti-inflammatory, and anti-thrombotic drugs is presented in Figure 1 below.

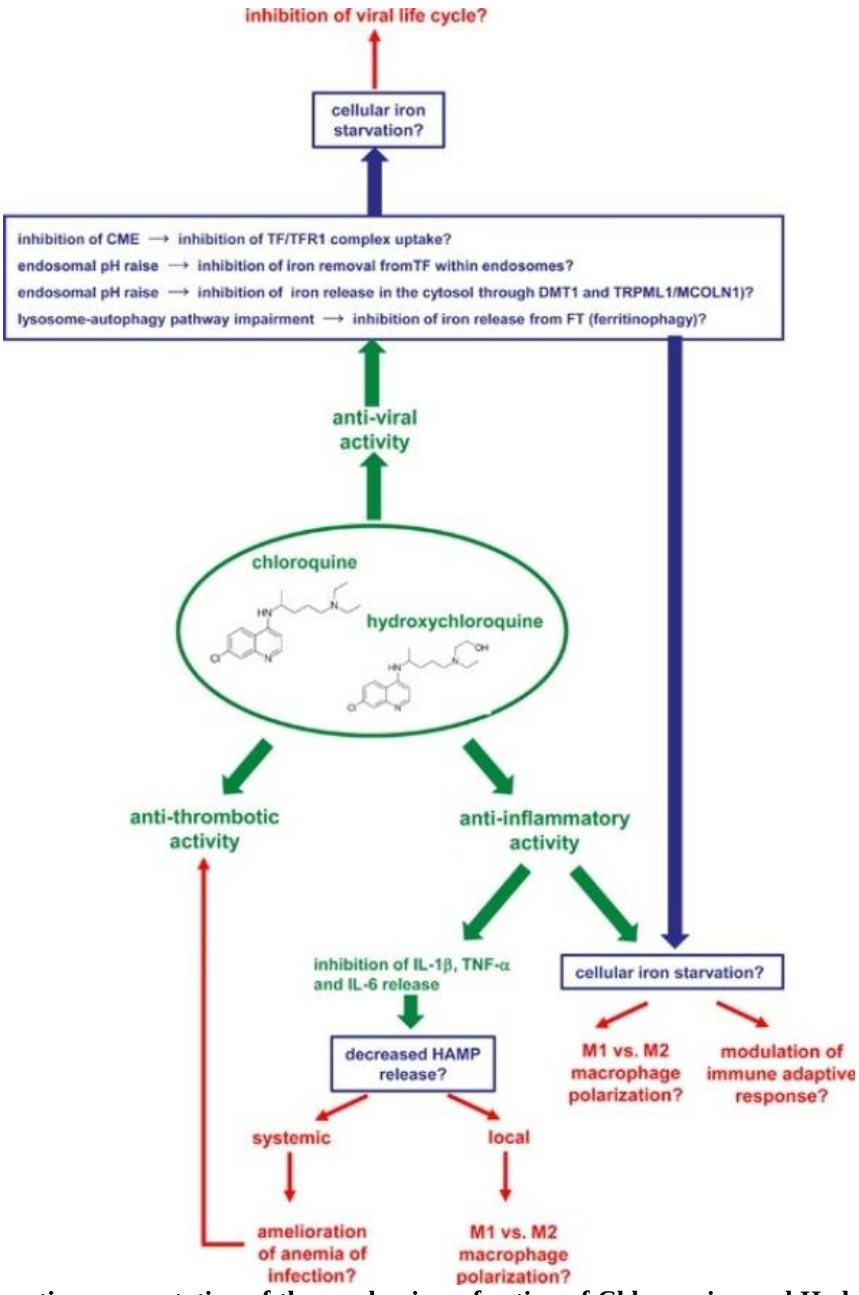

Figure 1: Diagrammatic representation of the mechanism of action of Chloroquine and Hydroxychloroquine as anti-viral, anti-inflammatory, and anti-thrombotic drugs and their links with systemic and cellular iron modulation (Roldan et al., 2020).

Mechanism of Action of Azithromycin

Azithromycin is a macrolide antibiotic used because of its ability to prevent bacterial protein synthesis by binding to the 50S subunit of the bacterial ribosome. Azithromycin has regulatory effects on immune cells. It decreases respiratory syncytial virus (RSV) release by reducing interferon signaling in vivo and inhibiting proinflammatory cytokine release in airway smooth muscle and epithelial cells (Parnham et al., 2014). Beyond its antibacterial activity, this macrolide has shown antiviral and immunomodulatory properties that could be of interest in viral infections, including SARS-Cov-2 (Echeverría-Esnal et al., 2021). Azithromycin may act on SARS-CoV-2 cleaving respiratory cells. Its intracellular build-up leads to an increase in the pH that may affect the trans-Golgi network (TGN) and lysosome functions (Nujić et al., 2012). The increase in the lysosomal pH by azithromycin affects the endocytosis process and lysosomal protease function (cathepsins or furins) (Ulrich and Pillat, 2020). Given that SARS-CoV-2 has been shown to present a furin-like cleavage site within the spike protein, the decrease in activation of Furins by azithromycin could inhibit the entry of SARS-CoV-2 into human epithelial cells (Nujić et al., 2012). The schematic representation of the mechanism of action of azithromycin is presented in Figure 2 below.

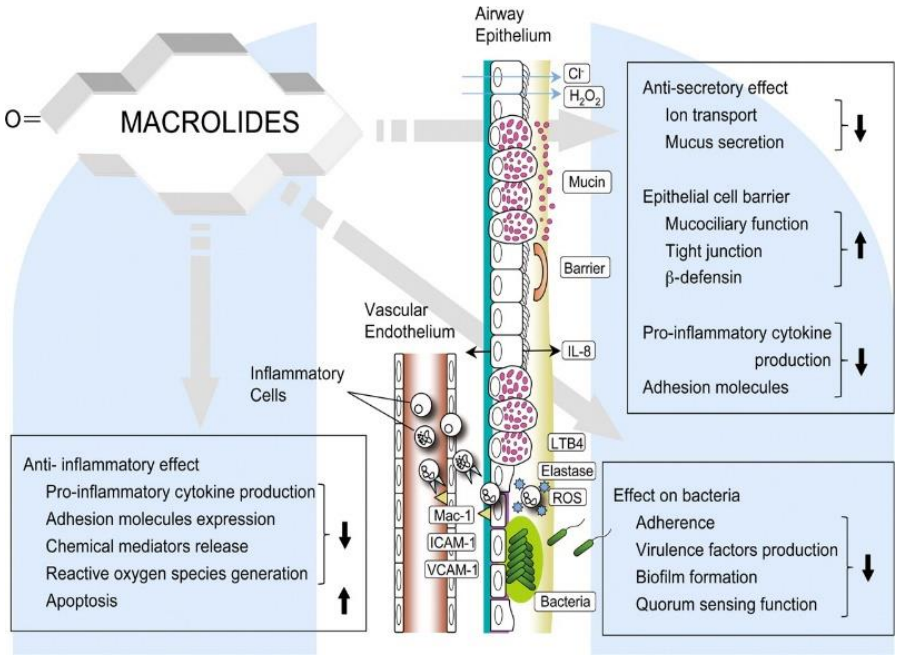

Figure 2: Schematic representation of the mechanism of action of Macrolides (Azithromycin) (Kanoh and Rubin, 2010).

Mechanism of Action of Remdesivir

Remdesivir is a prodrug metabolized to adenosine nucleotide analogues. The primary objective of nucleotide analogues is to inhibit the production of new viral RNA, thereby impeding infected host cells from serving as factories for new virions. Nucleotide analogues achieve this by incorporating a base into the replicating RNA strand that viral RNA polymerase cannot elongate from. It has demonstrated in vitro efficacy against SARS-CoV-2 (Wang et al., 2020c). Remdesivir is an inhibitor of RNA-dependent RNA polymerase (RdRp). It competes with adenosine triphosphate and absorbs into viral RNA chains (Cao et al., 2020). The Mechanism of action of Remdesivir is presented in Figure 3 below.

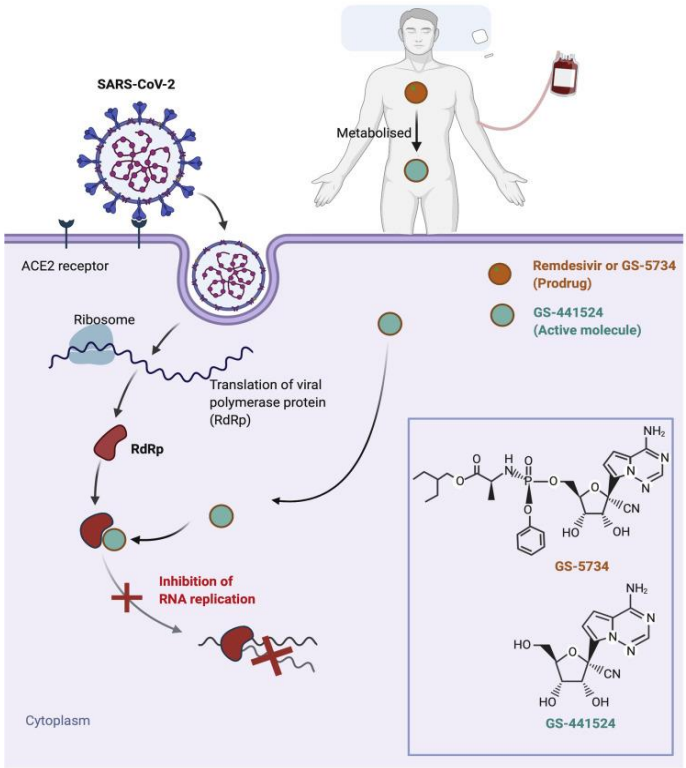

Figure 3: Mechanism of action of Remdesivir and its pharmacologically active form (GS-441524).(Frediansyah et al., 2021).

Mechanism of Action of Favipiravir

Favipiravir is a purine base analogue that undergoes intracellular phosphoribosylation to form active favipiravir ribofuranosyl-5'-triphosphate (favipiravir-RTP). It selectively and effectively inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. Favipiravir is integrated into the nascent viral RNA by error-prone viral RdRp, which results in chain termination and viral mutagenesis (Baranovich et al., 2013). The presence of favipiravir-RTP increases pressure on nucleotide content, particularly since the SARS-CoV-2 genome already has a low cytosine content. In total, along with the increased rate of mutation, favipiravir-RTP has an impact on SARS-CoV-2 by a cytopathic effect, which is caused by the virus, reducing the number of viral RNA, and infectious particles (Shannon et al., 2020). A schematic representation of the mechanism of action of Favipiravir in SARS-CoV-2 is captured in Figure 4 below.

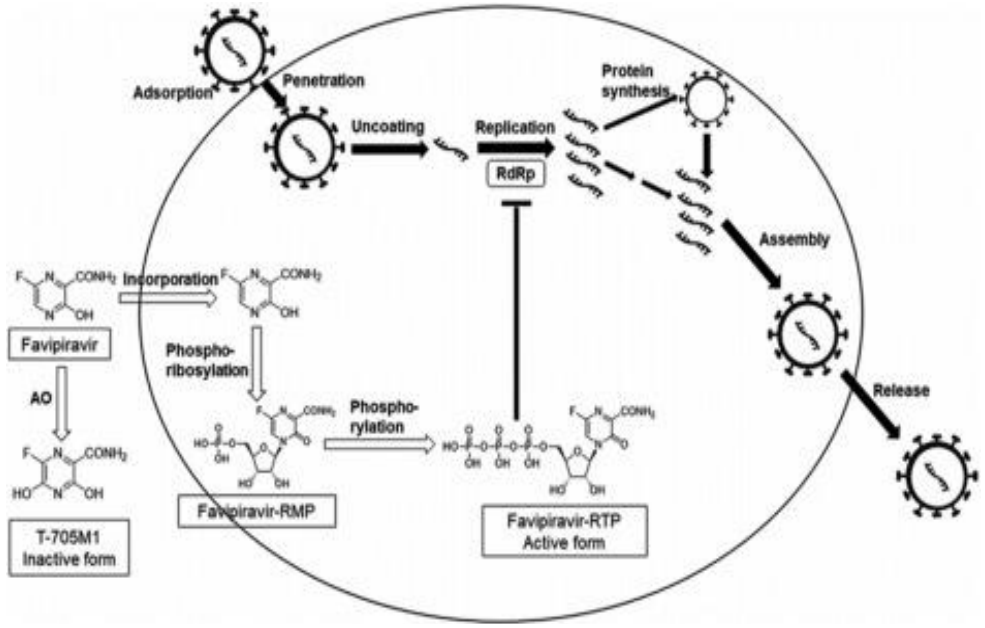

Fig. 4: Schematic representation of the mechanism of action of Favipiravir in SARS-CoV-2 (Joshi et al., 2021).

Mechanism of Action of Lopinavir/Ritonavir

Lopinavir and Ritonavir are Protease Inhibitors (PI's) that prevent infected cells from forming competent new virions by binding to and inactivating viral proteases to halt viral replication (Zhang et al., 2020). Protease inhibitors (PIs) competitively bind to the substrate site of viral proteases. These enzymes are responsible for the post-translational proteolysis of polyprotein precursors, enabling the release of functional viral proteins essential for replication, transcription, and maturation. Inhibition of these viral proteases result in the production of immature virus particles (Percha and Altman, 2013). Ritonavir is added to lopinavir as a pharmacokinetic booster (Chary et al., 2020). As a result of the low oral bioavailability of lopinavir and its extensive metabolism by the CYP3A4 isoenzyme, lopinavir is co-administered with ritonavir to attain drug concentrations high enough to prevent viral replication (Sheahan et al., 2020). The mechanism of action of Lopinavir/Ritonavir and Remdesivir is presented in Figure 5 below.

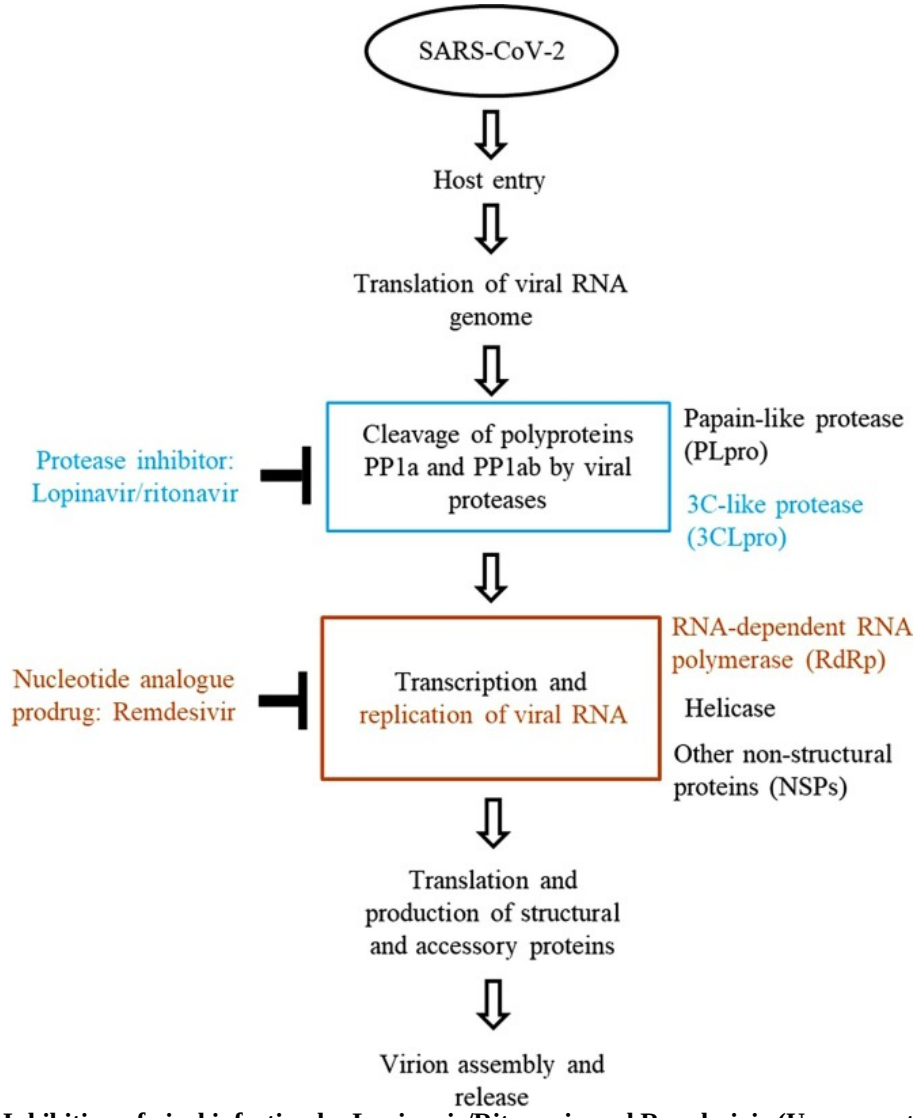

Figure 5: Inhibition of viral infection by Lopinavir/Ritonavir and Remdesivir (Uzunova et al., 2020).

LIFESTYLE FACTORS THAT AFFECT PHARMACOKINETICS OF DRUGS IN COVID-19 TREATMENT

Lifestyle may be seen as the daily activities of a people. These daily patterns include sleep patterns, pressure management strategies, eating propensities, and degrees of physical activity. Lifestyle could also be viewed regarding geographical locations, culture, and religion. All these factors influence the routine of a people. Reduced levels of mortality and morbidity have been linked with healthy and vigorous lifestyles (Balanzá–Martínez et al., 2020). The COVID-19 pandemic has histrionically impacted the unprecedented change in lifestyles globally. The constraint in movement, limited access to workout outfits, sedentary routines, social distancing, restricted access to health care, conscious increased hygiene levels, and poor nutrition levels have impacted greatly on stress levels (Ammar et al., 2021) and have led to adverse effects on mental health (Curtis et al., 2021) across many countries. A survey by (Ammar et al., 2021) showed that at the peak of the pandemic, many inclined towards unhealthy lifestyles leading to the increased burden of mental health globally (Fisher et al., 2020). While many people engaged in productive activities such as exploring new interests, better time management, and other coping adaptive mechanisms (Pigaiani et al., 2020) others engaged in activities such as smoking (Berlin et al., 2020) and increased alcohol intake (Curtis et al., 2021), unhealthy diets and sedentary lifestyles (Ammar et al., 2021) during the lockdown. But for the purpose of this study, we will look at substance abuse and excessive alcohol intake during this period.

PATHOPHYSIOLOGY OF CIGARETTE SMOKING AND OTHER SUBSTANCES ON COVID-19 TREATMENT

Cigarette smoking remains a crucial predisposing factor to a variety of respiratory diseases and mortalities recorded worldwide. Cigarette smoke is split into the particulate phase which contains >1017 free radicals and the material phase >1015 free radicals (Ambrose and Barua, 2004). While some articles (Reddy et al., 2021) have linked cigarette smoking as a major risk factor for poor outcomes in COVID-19 progression in patients,

(Lippi and Henry, 2020) claimed there was no connection between smoking and the progression of COVID-19. On the other hand, (Usman et al., 2020) suggested that active smokers were not adequately represented among COVID-19 patients. Also (Lippi and Henry, 2020; Lo and Lasnier, 2020) claim that cigarette smoking has protective effects against COVID-19. All these results create inconsistencies and do not allow for firm conclusions. This paradox could be attributed to the anti-inflammatory effect of nicotine (Ruan et al., 2020b) and the increased presence of nitric oxide gas (Usman et al., 2020). Although the link between cigarette smoking and disease progression is not fully known, existing data suggest a powerful link between smoking and disease progression (Huttunen et al., 2011; Reddy et al., 2021) Active smokers are at high risk of contracting COVID-19 thanks to certain unhygienic practices by smokers such as hand to mouth movements and inhalation (Berlin et al., 2020). Smokers are exposed to significant adverse effects on their respiratory tracts such as invasive pneumococcal disease, tuberculosis, influenza, and meningococcal diseases. Another health complication that results from smoking habits is Chronic obstructive pulmonary disease (COPD) (Huttunen et al., 2011) which is a major risk factor in COVID-19 progression (Berlin et al., 2020). A meta-analysis (Patanavanich and Glantz, 2020) indicated that smokers had 1.91 times the odds of COVID-19 severity progression compared to patients who had never smoked. The results of 11590 COVID-19 patients were analyzed, and the disease progressed in 18.4%, of which 6.3% had a smoking history. Of the cohort with a smoking history, 29.8% resulted in disease progression while only 17.7% of the non-smoking cohort progressed.

Another review by (Berlin et al., 2020) showed that current smokers and former smokers (22%) were in danger of having severe symptoms, mechanical ventilator use, and possible death compared to non-severe cases (13%). A systematic review showed that active smokers had a heightened risk of coming down with severe diseases than never or former smokers and are twofold more likely to have severe disease progression (Reddy et al., 2021) which agrees with (Patanavanich and Glantz, 2020). Tobacco smoke represses the functions of the innate immune system and makes smokers susceptible to infections (Melamed et al., 2020; Usman et al., 2020) and certain pathways such as the endocrine pathways and the neural circuits overlap in these processes (Melamed et al., 2020). Low doses of substance use stimulate the immune cells and, in some cases, cause apoptosis of immune cells, deterioration of the thymus and spleen, and repression of production of B and T cells. Some substances like opioids are shown to suppress the immune system through the hypothalamic-pituitary-adrenal axis as validated by some epidemiological studies. Many months of high doses of some substances like opioids exacerbate the progression of COVID-19 to the organ phase by damaging the lung's alveolar and degenerates with bacterial secondary infections (Ataei et al., 2020). There are about three phases of COVID-19 which include viral replication, adaptive immune stimulation, and pulmonary phase, and also the hypercoagulopathy, hyper-inflammatory, and organ damage phase (Ataei et al., 2020). The Angiotensin-converting enzyme-2 receptor (ACE-2) in the mucosa which is a receptor for both SARS-CoV-1 and SARS-CoV-2 and other coronaviruses is up-regulated in smokers making them prone to infections (Berlin et al., 2020; Brake et al., 2020). The expression of ACE2 protein is at the surface of lung type-2 pneumocytes (Brake et al., 2020) and it increases attachment of the virus to the mucosa and subsequent entry into the cell. Reduced expression of ACE reduces the breakdown of angiotensin 2 which increases the danger of local inflammation, vasoconstriction, thrombosis (Usman et al., 2020), and epithelial penetrability (Berlin et al., 2020; Matos et al., 2021).

Studies show that in some disease phases, inflammatory torrents and cytokine storms are present. Cytokines such as IL-2, IL-7, IL-10, and TNF-α are markers in life-threatening cases of COVID-19. Oftentimes, the domino effect of hyperinflammation is a multi-organ failure and eventual death (Ataei et al., 2020). However, inhibiting the activity of Janus Kinases (JAK) which is responsible for cytokine signalling using baricitinib may suppress the immune system and alter cellular viral entry and inflammation (Ataei et al., 2020). In a study of COVID-19 patients (Ye et al., 2020), the average levels of IL-6 were three times higher in severe cases compared to non-complicated cases. Viral infection resolution is facilitated by the CD4+ / CD8+ T cells and in smokers, there are increased levels of CD4+ / CD8+ T cells and lower levels of CD8+ lymphocytes from sputum analysis after retroviral therapy (Matos et al., 2021) which could lead to deteriorating cases in smokers. The CD4+ /CD8+ T cells recognize and target an antigen, and become activated to kill infected cells by some major pathways such as secreting anti-viral microbial cytokines, the IFN-y and TNF-α, (Berlin et al., 2020) and producing two cytotoxic granules, the granzymes and perforin to shut down the production of viral proteins and form a pore in the membrane of the target cell leading to apoptosis (Matos et al., 2021).

Overall, epidemiological studies show that cigarette smokers and persons with SUD are highly susceptible to COVID-19 infections and these groups should be monitored carefully as a vulnerable group. The pandemic caused a shift towards continuous use of substances by persons with substance use disorders (Melamed et al., 2020). This could be attributed to the lockdown, mental distress, poor access to healthcare services, and remote counsel and care from clinicians using telehealth (the use of phones, emails, video calls, and the internet to access healthcare) (Legha et al., 2020; Melamed et al., 2020). These have increased the need to smoke especially in the disadvantaged class. In the future, more data is needed to firmly ascertain the relationship between tobacco smoke,

SUD, and severity of the COVID-19 and their recovery rate. Smoking cessation should be encouraged especially among smokers with comorbidities and intervention campaigns should also be promoted by healthcare providers.

PATHOPHYSIOLOGY OF ALCOHOL ON COVID-19 TREATMENT

The heavy use of alcohol has very adverse effects on almost all organs of the body. Alcohol has a toxic effect on the body and reduces the efficacy of the body's immune system and its ability to cope with infectious agents. Evidence suggests that the intake of alcohol significantly increased in many countries during the COVID-19 pandemic (Delirrad and Mohammadi, 2020; Grossman et al., 2020; Pollard et al., 2020) to mitigate the stress of isolation during this period. The increased levels of alcohol consumption have generally led to stress-induced alcohol dependence and alcohol abuse (Grossman et al., 2020). Another research by Grossman et al. (2020) claimed there was no difference in alcohol consumption between males and females, (Rehm et al., 2020) suggested that alcohol consumption in males during the pandemic increased significantly. This claim is supported by another study that showed that there were more men with alcohol use disorder (AUD) who were more likely to have severe COVID-19 progression requiring the intensive care unit (ICU) (Da et al., 2020).

A study in Germany (Koopmann et al., 2020) suggested that more people reported no change in their alcohol consumption levels while those who reported an increase in alcohol consumption were mostly the low-educated population. (Delirrad and Mohammadi, 2020) alleged that false information on the potential prevention of COVID-19 infection and the Government's neglect to provide reliable information on the pandemic contributed to the increase in alcohol consumption as in the case of the methanol poisoning outbreak in Iran considering that it is a country where alcohol is not freely sold and consumed. Alcohol acts on both the innate and acquired immunity of a person. Experiments show that the T-cells and B cells and their functions are greatly reduced in chronic consumers of alcohol and there is also an increase in apoptosis and inhibition of T-cell activation (Simou et al., 2018) which can lead to community-acquired pneumonia (Testino et al., 2021a; Testino et al., 2021b) It was generally observed that patients with respiratory tract infections generally have gut dysfunctions (Gao et al., 2020) even though the link has not been well established. The most prominent comorbidities associated with alcohol consumption are hepatotoxicity, chronic liver disease, liver transplantation, and acute alcoholic hepatitis (AH) (Zelman et al., 2020). The liver is a potential target for COVID-19 because of the presence of ACE2 in the liver epithelial cells and biliary duct. The association between alcohol-related liver cirrhosis and SARS-CoV-2 has not been extensively studied. (Fix et al., 2020) showed that liver cirrhosis is associated with COVID-19 progression. There is a dose-response association between pneumonia and increasing alcohol intake and some of the drugs used for the treatment of COVID-19 such as tocilizumab and remdesivir which are suspected to be hepatotoxic (Fix et al., 2020) Steroids have been used in the treatment of AH but has shown degenerated outcomes in patients with AH and COVID-19. This is because steroids are immunosuppressants and leave the patients more susceptible to infection (Zelman et al., 2020) hepatic decompensation and injury caused by COVID-19 include ischemia, cytokine storms, and direct viral infections and these are injurious to the liver (Da et al., 2020).

The government and healthcare providers play a major role in managing the increased consumption of alcohol, substance use, and their long-term effects (Koopmann et al., 2020). While policies could be made to monitor and restrict access to liquor and other substances as these have detrimental effects on health in the long run the possibility of people having severe withdrawal symptoms may be high (Ramalho, 2020; Rehm et al., 2020). Therefore, there should be a balance to combat both extremes. Telehealth is a new process that has been adopted by many healthcare facilities to mitigate the spread of COVID-19 infection and emergency response. More research is needed to validate the actual response of patients who use telehealth as their primary access to healthcare as compared with those who have had in-person healthcare delivery.

TOXICITIES ASSOCIATED WITH THERAPEUTIC OPTIONS

Chloroquine and hydroxychloroquine

Chloroquine, including its sulfate and phosphate salts, is a drug used for the prevention and treatment of malaria. Due to its possible antiviral activity and relatively mild side effects (Touret and deLamballerie, 2020) Chloroquine has been proposed as a secondary treatment option for SARS-CoV-2 infections (Tingbo, 2021). In 2018, the Royal College of Ophthalmologists issued guidelines for screening for retinotoxicity in patients using chloroquine and hydroxychloroquine. Many patients are prescribed 400 mg of hydroxychloroquine daily, which exceeds the recommended dosage for individuals weighing less than 80 kg. Emerging evidence indicates an increased risk of retinopathy in patients taking more than 5 mg/kg of hydroxychloroquine daily. Prescribers should be aware of the recommendations regarding hydroxychloroquine dosage (less than 5 mg/kg daily), even though no dose is absolutely safe (Yusuf et al., 2018).

A study issued in 2019 found that glial cell damage was due to the production of reactive oxygen species, with decreased glutamate utilization. The damage was lowered when ascorbic acid was added to cell cultures (Oliveira et al., 2019). Chloroquine, when deposited in the cornea, can cause opacities in the posterior subcapsular part of the lens, abnormalities in the ciliary body, and macular pigmentation disorders. These effects

may manifest as partial vision loss and blurred vision. The mechanism of injury could involve the binding of chloroquine to melanin in retinal pigment epithelium, which would eventually lead to cell migration to other retinal layers, irreparable photoreceptor loss, and waste of retinal pigment epithelium (Arndt et al., 2018). Chloroquine has a long elimination half-life (approximately one month), whereas total eradication takes about 6 months (Hickley et al., 2011; Kalia and Dutz, 2007).

Chloroquine crosses the placental barrier, but there is no evidence suggesting that it causes harm to the foetus. It is also excreted through breast milk (Rainsford et al., 2015). A study in laboratory mice found that it stockpiles in the retina of pups, but the accumulation was temporary and did not cause permanent damage (Ullberg et al., 1970). In addition to visual damage, chloroquine administration may lead to side effects such as dizziness, headache, nausea, vomiting, diarrhoea, and skin rash. The most serious concern associated with chloroquine is cardiac arrest, underscoring the recommendation for structured electrocardiographic monitoring. In a recent study, it was proposed that chloroquine prolonged corrected QT interval (QTc) significantly (van den Broek et al., 2020). It should not be administered to individuals with a history of arrhythmia, retinal impairment, or hearing impairment (Tingbo, 2020).

Remdesivir

Remdesivir is a broad-spectrum antiviral precursor that reacts as an adenosine nucleotide counterpart, used for Ribonucleic acid virus infections therapy (Wang et al., 2020b). According to a recent study by Grein et al. (2020), common adverse effects associated with remdesivir administration in COVID-19 patients included elevated liver enzymes, low blood pressure, renal impairment, rash, and diarrhoea. Patients received an initial dose of 200 mg intravenously on the first day, followed by 100 mg daily for the next nine days. Adverse effects were reported in 60% of subjects, with serious complications such as acute renal injury, low blood pressure, septic shock, and multiple organ dysfunction syndrome observed in 12% of subjects. Four patients stopped the therapy because of multiple organ failure, increased hepatic enzymes, and maculopapular rash (Grein et al., 2020).

In vitro studies indicate that remdesivir-induced liver toxicity is attributed to increased membrane permeability and intracellular drug metabolism. Experimental studies have shown that remdesivir can increase respiratory rate in animals, with no observed effects on central nervous system (CNS) and cardiovascular function. Interestingly, in toxicity studies involving animals treated with remdesivir for four weeks, kidneys were identified as the primary organs affected by toxicity. No changes in liver function were noticed in rats and cynomolgus monkeys (WHO, 2021).

Ritonavir

Ritonavir is a member of a new protease antagonist that was approved in 2000 by the FDA (Chandwani and Shuter, 2008; Lv et al., 2015). In a prospective unit study that involves approximately 300 subjects, the initial treatment with ritonavir resulted in liver toxicity in 30% of patients (95% confidence interval 17.9–44.6%) (Nolan et al., 2005; Sulkowski et al., 2000) Liver toxicity was assessed by observing the activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The odds ratio for liver toxicity following ritonavir administration in a complete dose i.e. 400 mg was 6.2 (95% confidence interval 2.8–13.7) (Sulkowski et al., 2000). Liver toxicity associated with protease inhibitor drugs can manifest through non-specific gastrointestinal symptoms such as upper and lower abdominal pain, nausea, vomiting, and diarrhoea. Additional symptoms may include jaundice and hepatomegaly. Shortly after initiating protease inhibitor treatment, several cases of recurrent and severe bleeding were observed in patients with haemophilia. The specific mechanisms underlying this bleeding phenomenon have not yet been fully understood. Some of the places where the bleeding occurred were the small joints of the hands as well as the soft tissue of the palms (Nolan et al., 2005).

Dyslipidaemia associated with antiretroviral treatment is characterized by elevated total cholesterol, reduced high-density lipoprotein (HDL) cholesterol levels, increased triglycerides, and elevated low-density lipoprotein (LDL) cholesterol levels These results of protease inhibitors were described by the binding of lipoprotein particles or the blocking of their binding to the LDL receptor, which disturbs the mechanisms accountable for intracellular synthesis, storage and release of cholesterol l(Nolan et al., 2005). Administration of the treatment from the protease antagonist group ends up in sequestration of endoplasmic reticulum-derived transcription factor that are involved in lipogenesis and to deficiency of adiponectin (Lv et al., 2015). The inhibition of proteasomal degradation of apolipoprotein B is another mechanism that is related to the onset of dyslipidaemia in patients who are given this group of drugs (Anđelković et al., 2016; Lv et al., 2015).

Umifenovir

Umifenovir (registered as Arbidol) is a Ribonucleic acid (RNA) polymerase antagonist approved for the treatment of influenza only in Russia and China. Thanks to its mechanism of action, the drug was seen as a potential therapy for novel SARS-CoV-2 infection (Chen et al., 2020). Umifenovir has been shown to be safe, even to be used in pregnant women, and showed no teratogenic effects (Rasmussen et al., 2012). Umifenovir exhibits an exceptionally wide therapeutic index, suggesting it is likely to be well tolerated. Administration of 200 mg to volunteers demonstrated excellent tolerability. Extended use over several days to at least one month has also been well tolerated. A study showed no toxic effect

occurrences during chronic administration of this drug (Blaising et al., 2014). Certain adverse effects were recorded, importantly gastrointestinal adverse effects and increased transaminase levels (Wang et al., 2010). In a test of umifenovir and paracetamol combination toxicity in experimental animals, orally, no observed adverse effect level (NOAEL) was determined at 200 mg/kg per day (Wang et al., 2010). Also, another study showed a safe dose of umifenovir at 350 mg/kg, although, weight loss and hair loss occurred at a dose of 1200 mg/kg. Indistinguishable data were obtained in other studies (Blaising et al., 2014).

Convalescent Plasma

Convalescent plasma refers to pooled plasma or immunoglobulins collected from individuals who have previously been infected and recovered from a disease. In 10 patients seropositive for SARS-CoV-2and hypoxic, but not intubated, 1 dose of 200 mL of convalescent plasma led to a nearly instant undetectable viral load and better oxygenation in 3 days (Duan et al., 2020). In 5 patients who were intubated with radiographic proof of acute lung injury, transfusion of 200–250 mL of convalescent plasma on days 10 and 22 of admission reduced hypoxia in all 5 and 3 were able to be weaned from mechanical ventilation (Shen et al., 2020b). Risks commonly associated with plasma transfusion include:

1. Transfusion-associated acute lung injury (TRALI)
2. Transfusion-associated circulatory overload (TACO)
3. Allergic or anaphylactic reactions

Other less common risks include

1. Transmission of infections,
2. Febrile non-haemolytic transfusion reactions,
3. Red blood cell alloimmunization, and
4. Haemolytic transfusion reactions (Pandey and Vyas, 2012).

A meta-analysis of studies that used convalescent plasma to treat severe acute respiratory syndrome (SARS) and influenza A (H1N1) detailed no adverse effects beyond minor infusion reactions such as chills and fevers (Mair-Jenkins et al., 2014). 4 critically ill patients with SARSCoV-2 had no notable adverse events when treated with convalescent plasma and supportive care (Zhang et al., 2020).

Umifenovir

Umifenovir (registered as Arbidol) is a Ribonucleic acid (RNA) polymerase antagonist approved for the treatment of influenza only in Russia and China. Thanks to its mechanism of action, the drug was seen as a potential therapy for novel SARS-CoV-2 infection (Chen et al., 2020). Umifenovir has shown to be safe, even to be used in pregnant women, and showed no teratogenic effects (Rasmussen et al., 2012). The therapeutic index of Umifenovir is incredibly broad, thus it can be anticipated that it will be well tolerated. Administration of 200 mg to volunteers showed excellent tolerability. The usage over several days to at least one month was also well tolerated.

A study showed no toxic effect during chronic administration of this drug (Blaising et al., 2014). Certain adverse effects were recorded, importantly gastrointestinal adverse effects and increased transaminase levels (Wang et al., 2010). In a test of umifenovir and paracetamol combination toxicity in experimental animals, orally, no observed adverse effect level (NOAEL) was determined at 200 mg/kg per day (Wang et al., 2010). Also, another study showed a safe dose of umifenovir at 350 mg/kg, although, weight loss and hair loss occurred at a dose of 1200 mg/kg. Indistinguishable data were obtained in other studies (Blaising et al., 2014).

In conclusion, the urgent need for effective COVID-19 therapies has driven pharmaceutical companies to develop new treatments or repurpose existing ones against SARS-CoV-2. Frontline healthcare providers may lack familiarity with older treatments such as chloroquine or specialized drugs like DNA vaccines, protease inhibitors, and convalescent plasma. Alongside effective infection control policies, a strategic and thoughtful repurposing of existing treatments, the development and rigorous evaluation of new medications, and guidance from medical toxicologists may reduce morbidity and mortality from COVID-19, preventing scenarios where the treatment causes more harm than the disease.

TOXIC EFFECTS ASSOCIATED WITH CO-ADMINISTRATION OF DRUGS DURING COVID-19 TREATMENT

Lopinavir/ritonavir + umifenovir

The combination of lopinavir and ritonavir with umifenovir was one of the 1st choices for the treatment of COVID-19 described in the Handbook based on clinical experience in the 1st Affiliated Hospital, Zheijang University School of Medicine (Tingbo 2020). However, this approach is associated with liver damage in approximately 50% of treated patients, characterized by elevated serum aminotransferase enzymes and jaundice. On the contrary, in the retrospective cohort study, researchers described that this combination of medicines was more effective than the lopinavir/ritonavir combination but led to close adverse effects: higher bilirubin levels, mild diarrhea, and vomiting (Deng et al., 2020).

Lopinavir/ritonavir + interferon beta

A clinical trial titled "Middle East Respiratory Syndrome with a merger of lopinavir, ritonavir and Interferon Beta-1b (MIRACLE trial)" is anticipated to examine the efficacy and safety of a given medicine combination in the therapy of MERS-CoV coronavirus infection originally recorded in 2012. The dosage used in this work will include 400/ 100 mg of lopinavir/ritonavir as 5 mL suspension applied via nasogastric tube and 0.25

mg/mL of interferon beta-1b applied subcutaneously (Arabi et al., 2018). The authors indicate that lopinavir is utilized to extend the half-life of ritonavir and to explore the combination of lopinavir and ritonavir with interferon beta in forthcoming studies. An update on the statistical analysis plan for the trial has been published not long ago. (Arabi et al., 2020).

Chloroquine + remdesivir

A recent in vitro study has demonstrated effective inhibition of SARS-CoV-2, suggesting potential use of the drugs in COVID-19 treatment (Wang et al., 2020b). However, there are currently no published data regarding the safety or efficacy of combining these medications.

Chloroquine + azithromycin

There is limited data available regarding the efficacy and safety of combining chloroquine and azithromycin for COVID-19 treatment. A study conducted in France reported that combined hydroxychloroquine and azithromycin treatment was more successful compared to untreated patients or those treated with hydroxychloroquine alone. Hydroxychloroquine was chosen, rather than chloroquine, because of its decreased toxicity, increased safety, and higher dose capability (Liu et al., 2020). The results of this study suggest a synergistic effect of the two drugs. The researchers noted that out of twenty treated patients, only six received azithromycin in combination with hydroxychloroquine to prevent bacterial superinfection, with daily monitoring of cardiac output by electrocardiogram due to the potential, albeit low, risk of prolonged QT interval.

The results of the above study regarding the safety of administered drugs have not yet been published (Gautret et al., 2020b). These results pertain to the administration of 200 mg of hydroxychloroquine sulfate orally three times daily for 10 days, alongside 500 mg of azithromycin on the first day followed by 250 mg daily for the next 4 days, with continuous electrocardiogram (ECG) monitoring. In an animal study based on a model of heart instability in guinea pigs, azithromycin alone or in combination with chloroquine did not give rise to a proarrhythmogenic effect, unlike the administration of chloroquine alone (Fossa et al., 2007) The combination of chloroquine and azithromycin has been previously used in clinical trials in Africa for malaria treatment, demonstrating safety. In one trial, only one patient experienced a serious side effect of vomiting.

FUTURE PERSPECTIVES

The COVID-19 pandemic has highlighted critical areas requiring further research and development to better manage and eventually overcome the global health crisis. One significant area is the continuous monitoring and understanding of SARS-CoV-2 mutations, which can influence the efficacy of existing vaccines and treatments. Enhanced genomic surveillance is essential to track these changes and adapt strategies accordingly.

The development of new therapeutic agents remains paramount. While current antiviral drugs like remdesivir and chloroquine have shown some efficacy, there is an urgent need for more potent and specific antiviral therapies. Additionally, understanding the long-term effects of COVID-19 on different organ systems, particularly in post-acute sequelae of SARS-CoV-2 infection (PASC), also known as long COVID, is critical. Comprehensive longitudinal studies are necessary to elucidate the full spectrum of long-term complications and to develop targeted treatment protocols.

The role of host immune response in disease progression and outcomes should also be a focal point of future research. Investigating the mechanisms underlying severe inflammatory responses and potential therapeutic interventions to modulate the immune response could improve patient outcomes.

Finally, the adoption of telehealth and its impact on healthcare delivery warrants further study. Evaluating patient outcomes and satisfaction with telehealth compared to traditional in-person visits can inform future healthcare models, ensuring accessibility and efficiency while maintaining high standards of care. Overall, a multidisciplinary approach involving continuous research, global collaboration, and adaptive healthcare strategies is essential to effectively combat COVID-19 and prepare for future pandemics.

CONCLUSION

The COVID-19 pandemic has presented unprecedented challenges, but it has also accelerated advancements in medical research and healthcare delivery. The investigation into the efficacy of various antiviral treatments, such as remdesivir and hydroxychloroquine, has highlighted the complexities of managing viral infections. While initial results showed promise, further research is essential to confirm their long-term benefits and potential side effects.

The pandemic has underscored the importance of genomic surveillance in tracking viral mutations and understanding their impact on vaccine effectiveness and disease spread. Continuous monitoring and rapid adaptation of vaccines are crucial in combating emerging variants. In conclusion, a multidisciplinary approach, integrating continuous research, innovation in therapeutic strategies, and adaptive healthcare delivery models, is essential for managing such pandemic and preparing for future public health crises.

REFERENCES

1. Ambrose, J. A., & Barua, R. S. The pathophysiology of cigarette smoking and cardiovascular disease. Journal of the American College of Cardiology, 2004; 43(10): 1731–1737. https://doi.org/10.1016/j.jacc.2003.12.047
2. Ammar, A., Trabelsi, K., Brach, M., Chtourou, H., Boukhris, O., Masmoudi, L., Bouaziz, B., Bentlage,

E., How, D., Ahmed, M., Mueller, P., Mueller, N., Hammouda, O., Paineiras-Domingos, L., Braakman-jansen, A., Wrede, C., Bastoni, S., Pernambuco, C., Mataruna, L., … Hoekelmann, A. Effects of home confinement on mental health and lifestyle behaviours during the COVID-19 outbreak: Insight from the ECLB-COVID19 multicenter study. Biology of Sport, 2021; 38(1): 9–21. https://doi.org/10.5114/biolsport.2020.96857

3. Anđelković, M., Buha, A., Vukomanović, P., & Matović, V. (2016). Safety of antiretroviral drugs. Arhiv Za Farmaciju, 66(4): 161–173. https://doi.org/10.5937/ARHFARM1604161A
4. Arabi, Y. M., Alothman, A., Balkhy, H. H., Al-Dawood, A., AlJohani, S., al Harbi, S., Kojan, S., al Jeraisy, M., Deeb, A. M., Assiri, A. M., Al-Hameed, F., AlSaedi, A., Mandourah, Y., Almekhlafi, G. A., Sherbeeni, N. M., Elzein, F. E., Memon, J., Taha, Y., Almotairi, A., … Hussein, M. A. (2018). Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial. Trials., 2018; 19: 1, 19(1): 1–13. https://doi.org/10.1186/S13063-017-2427-0
5. Arabi, Y. M., Asiri, A. Y., Assiri, A. M., Aziz Jokhdar, H. A., Alothman, A., Balkhy, H. H., AlJohani, S., al Harbi, S., Kojan, S., al Jeraisy, M., Deeb, A. M., Memish, Z. A., Ghazal, S., al Faraj, S., Al-Hameed, F., AlSaedi, A., Mandourah, Y., al Mekhlafi, G. A., Sherbeeni, N. M., … Hussein, M. A. (2020). Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon-β1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial. Trials., 2020; 21(1): 1–8. https://doi.org/10.1186/S13063-019-3846-X
6. Arndt, C., Costantini, M., Chiquet, C., Afriat, M., Berthemy, S., Vasseur, V., Ducasse, A., & Mauget-Faÿsse, M. (2018). Comparison between multifocal ERG and C-Scan SD-OCT ("en face" OCT) in patients with a suspicion of antimalarial retinal toxicity: preliminary results. Documenta Ophthalmologica, 2018; 136(2): 97–111. https://doi.org/10.1007/S10633-018-9625-2
7. Ataei, M., Shirazi, F. M., Lamarine, R. J., Nakhaee, S., & Mehrpour, O. A double-edged sword of using opioids and COVID-19: a toxicological view. Substance Abuse Treatment, Prevention, and Policy, 2020; 15(1): 91. https://doi.org/10.1186/s13011-020-00333-y
8. Balanzá–Martínez, V., Atienza–Carbonell, B., Kapczinski, F., & De Boni, R. B. Lifestyle behaviours during the COVID-19 – time to connect. Acta Psychiatrica Scandinavica, 2020; 141(5): 399–400. https://doi.org/10.1111/acps.13177
9. Baranovich, T., Wong, S. S., Armstrong, J., Marjuki, H., Webby, R. J., Webster, R. G., & al., et. T-705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro. J Virol, 2013; 87: 3741–3751.
10. Berlin, I., Thomas, D., Le Faou, A.-L., & Cornuz, J. COVID-19 and Smoking. Nicotine & Tobacco Research, 2020; 22(9): 1650–1652. https://doi.org/10.1093/ntr/ntaa059
11. Blaising, J., Polyak, S. J., & Pécheur, E. I. Arbidol as a broad-spectrum antiviral: An update. Antiviral Research, 2014; 107(1): 84–94. https://doi.org/10.1016/J.ANTIVIRAL.2014.04.006
12. Boone, B. A., Murthy, P., Miller-Ocuin, J., Doerfler, W. R., Ellis, J. T., Liang, X., Ross, M. A., Wallace, C. T., Sperry, J. L., Lotze, M. T., Neal, M. D., & Zeh, H. J. Chloroquine reduces hypercoagulability in pancreatic cancer through inhibition of neutrophil extracellular traps. BMC Cancer, 2018; 18(1). https://doi.org/10.1186/S12885-018-4584-2
13. Brake, S. J., Barnsley, K., Lu, W., McAlinden, K. D., Eapen, M. S., & Sohal, S. S. Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). Journal of Clinical Medicine, 2020; 9(3): 841. https://doi.org/10.3390/jcm9030841
14. Cao, Y. chen, Deng, Q. xin, & Dai, S. xue. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Medicine and Infectious Disease, 2020; 35. https://doi.org/10.1016/J.TMAID.2020.101647
15. Chandwani, A., & Shuter, J. Lopinavir/ritonavir in the treatment of HIV-1 infection: a review. In Therapeutics and Clinical Risk Management, 2008; 4(5).
16. Chary, M. A., Barbuto, A. F., Izadmehr, S., Hayes, B. D., & Burns, M. M. COVID-19: Therapeutics and Their Toxicities. Journal of Medical Toxicology, 2020; 16(3): 284. https://doi.org/10.1007/S13181-020-00777-5
17. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet., 2020 Feb 15; 395(10223): 507-513. doi: 10.1016/S0140-6736(20)30211-7. Epub 2020 Jan 30. PMID: 32007143; PMCID: PMC7135076.
18. Chen, C., Zhang, Y., Huang, J., Yin, P., Cheng, Z., Wu, J., Chen, S., Zhang, Y., Chen, B., Lu, M., Luo, Y., Ju, L., Zhang, J., & Wang, X. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. MedRxiv, 2020. 2020.03.17.20037432. https://doi.org/10.1101/2020.03.17.20037432
19. Cui et al. Cui, J., Li, F., & Shi, Z. L. (2018). Origin and evolution of pathogenic coronaviruses. Nature Reviews Microbiology, 2018; 17(3): 181–192. https://doi.org/10.1038/s41579-018-0118-9.
20. Curtis, R. G., Olds, T., Ferguson, T., Fraysse, F., Dumuid, D., Esterman, A., Hendrie, G. A., Brown, W. J., Lagiseti, R., & Maher, C. A. Changes in diet,

activity, weight, and wellbeing of parents during COVID-19 lockdown. PLOS ONE, 2021; 16(3): e0248008. https://doi.org/10.1371/journal.pone.0248008

21. Da, B. L., Im, G. Y., & Schiano, T. D. Coronavirus Disease 2019 Hangover: A Rising Tide of Alcohol Use Disorder and Alcohol-Associated Liver Disease. Hepatology, 2020; 72(3): 1102–1108. https://doi.org/10.1002/hep.31307
22. David Gorski, MD, PhD: On "natural immunity" to COVID-19 (and every other vaccine-preventable disease) | weehingthong. (n.d.). Retrieved October 17, 2021, from https://weehingthong.org/2021/10/12/david-gorski-md-phd-on-natural-immunity-to-covid-19-and-every-other-vaccine-preventable-disease/
23. Delirrad, M., & Mohammadi, A. B. New Methanol Poisoning Outbreaks in Iran Following COVID-19 Pandemic. Alcohol and Alcoholism, 2020; 55(4): 347–348. https://doi.org/10.1093/alcalc/agaa036
24. Deng, L., Li, C., Zeng, Q., Liu, X., Li, X., Zhang, H., Hong, Z., & Xia, J. (2020). Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease A retrospective cohort study. Journal of Infection, 2019; 81(1): e1–e5. https://doi.org/10.1016/J.JINF.2020.03.002
25. Duan, K., Liu, B., Li, C., Zhang, H., Yu, T., Qu, J., Zhou, M., Chen, L., Meng, S., Hu, Y., Peng, C., Yuan, M., Huang, J., Wang, Z., Yu, J., Gao, X., Wang, D., Yu, X., Li, L., … Yang, X. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proceedings of the National Academy of Sciences, 2020; 117(17): 9490–9496. https://doi.org/10.1073/PNAS.2004168117
26. Duan, K., Liu, B., Li, C., Zhang, H., Yu, T., Qu, J., Zhou, M., Chen, L., Meng, S., Hu, Y., Peng, C., Yuan, M., Huang, J., Wang, Z., Yu, J., Gao, X., Wang, D., Yu, X., Li, L., … Yang, X. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proceedings of the National Academy of Sciences, 2020; 117(17): 9490–9496. https://doi.org/10.1073/PNAS.2004168117
27. Echeverría-Esnal, D., Martin-Ontiyuelo, C., Navarrete-Rouco, M. E., De-Antonio Cuscó, M., Ferrández, O., Horcajada, J. P., & Grau, S. Azithromycin in the treatment of COVID-19: a review. Expert Review of Anti-Infective Therapy, 2021; 19(2): 147–163. https://doi.org/10.1080/14787210.2020.1813024
28. Fehr, A. R., & Perlman, S. Coronaviruses: An overview of their replication and pathogenesis. Coronaviruses: Methods and Protocols, 2015; 1–23. https://doi.org/10.1007/978-1-4939-2438-7_1
29. Fisher, J. R., Tran, T. D., Hammarberg, K., Sastry, J., Nguyen, H., Rowe, H., Popplestone, S., Stocker, R., Stubber, C., & Kirkman, M. Mental health of people in Australia in the first month of <scp>COVID</scp> -19 restrictions: a national survey. Medical Journal of Australia, 2020; 213(10): 458–464. https://doi.org/10.5694/mja2.50831
30. Fix, O. K., Hameed, B., Fontana, R. J., Kwok, R. M., McGuire, B. M., Mulligan, D. C., Pratt, D. S., Russo, M. W., Schilsky, M. L., Verna, E. C., Loomba, R., Cohen, D. E., Bezerra, J. A., Reddy, K. R., & Chung, R. T. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. Hepatology, 2020; 72(1): 287–304. https://doi.org/10.1002/hep.31281
31. Fomnya, H. J., Ngulde, S. I., Gana, S. M., Bilbonga, G., Amshi, K. A., Midala, C. A. & Garba, K. A. Drug Repositioning in Response to COVID-19 and other Challenging Diseases. American Journal of Pharmacology and Toxicology, 2022; 17(1): 37-47. https://doi.org/10.3844/ajptsp.2022.37.47
32. Fossa, A. A., Wisialowski, T., Duncan, J. N., Deng, S., & Dunne, M. Azithromycin/Chloroquine Combination Does Not Increase Cardiac Instability despite an Increase in Monophasic Action Potential Duration in the Anesthetized Guinea Pig. The American Journal of Tropical Medicine and Hygiene, 2007; 77(5): 929–938. https://doi.org/10.4269/AJTMH.2007.77.929
33. Frediansyah, A., Nainu, F., Dhama, K., Mudatsir, M., & Harapan, H. Remdesivir and its antiviral activity against COVID-19: A systematic review. Clinical Epidemiology and Global Health, 2021; 9: 123. https://doi.org/10.1016/J.CEGH.2020.07.011
34. FURUTA et al. (2017): Furuta, Y., Komeno, T., & Nakamura, T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proceedings of the Japan, 2017.
35. Gao, Q. Y., Chen, Y. X., & Fang, J. Y. 2019 Novel coronavirus infection and gastrointestinal tract. Journal of Digestive Diseases, 2020; 21(3): 125–126. https://doi.org/10.1111/1751-2980.12851
36. Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V. E., Tissot Dupont, H., Honoré, S., Colson, P., Chabrière, E., la Scola, B., Rolain, J. M., Brouqui, P., & Raoult, D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents, 2020a; 56(1): 105949. https://doi.org/10.1016/J.IJANTIMICAG.2020.105949
37. Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V. E., Tissot Dupont, H., Honoré, S., Colson, P., Chabrière, E., la Scola, B., Rolain, J. M., Brouqui, P., & Raoult, D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents, 2020b; 56(1): 105949. https://doi.org/10.1016/J.IJANTIMICAG.2020.105949
38. Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A., Feldt, T., Green, G.,

Green, M. L., Lescure, F.-X., Nicastri, E., Oda, R., Yo, K., Quiros-Roldan, E., Studemeister, A., Redinski, J., Ahmed, S., Bernett, J., Chelliah, D., … Flanigan, T. Compassionate Use of Remdesivir for Patients with Severe Covid-19. Https://Doi.Org/10.1056/NEJMoa2007016, 2020; 382(24): 2327–2336. https://doi.org/10.1056/NEJMOA2007016

39. Grossman, E. R., Benjamin-Neelon, S. E., & Sonnenschein, S. Alcohol Consumption during the COVID-19 Pandemic: A Cross-Sectional Survey of US Adults. International Journal of Environmental Research and Public Health, 2020; 17(24): 9189. https://doi.org/10.3390/ijerph17249189
40. Guan et al. (2020a): Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine, 2020; 382(18): 1708–1720. https://doi.org/10.1056/NEJMoa2002032.
41. Guerriero JL. Macrophages: Their Untold Story in T Cell Activation and Function. Int Rev Cell Mol Biol., 2019; 342: 73-93. doi: 10.1016/bs.ircmb.2018.07.001. Epub 2018 Aug 1. PMID: 30635094.
42. Heidary, F., & Gharebaghi, R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. The Journal of Antibiotics, 2020; 73(9): 593–602. https://doi.org/10.1038/s41429-020-0336-z
43. Hickley, N. M., Al-Maskari, A., & McKibbin, M. Chloroquine and Hydroxychloroquine Toxicity. Archives of Ophthalmology, 2011; 129(11): 1506–1507. https://doi.org/10.1001/ARCHOPHTHALMOL.2011.321
44. Holshue et al. Holshue, M. L., DeBolt, C., Lindquist, S., Lofy, K. H., Wiesman, J., Bruce, H., et al. (2020). First Case of 2019 Novel Coronavirus in the United States. New England Journal of Medicine, 2020; 382(10): 929–936. https://doi.org/10.1056/NEJMoa2001191.
45. Hu et al. (2020): Hu, C., Lu, Y., Wang, M., & Zhang, W. Clinical efficacy and safety of interferon-α2b in the treatment of COVID-19: A multicenter, randomized controlled trial. Journal of the American Medical Association, 2020; 323(11): 1034-1035. https://doi.org/10.1001/jama.2020.0732.
46. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet., 2020 Feb 15; 395(10223): 497-506. doi: 10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24. Erratum in: Lancet., 2020 Feb 15; 395(10223): 496. doi: 10.1016/S0140-6736(20)30252-X. PMID: 31986264; PMCID: PMC7159299.
47. Hung, I. F., To, K. K., Lee, C.-K., Lee, K.-L., Chan, K., Yan, W.-W., Liu, R., Watt, C.-L., Chan, W.-M., Lai, K.-Y., Koo, C.-K., Buckley, T., Chow, F.-L., Wong, K.-K., Chan, H.-S., Ching, C.-K., Tang, B. S., Lau, C. C., Li, I. W., … Yuen, K.-Y. Convalescent Plasma Treatment Reduced Mortality in Patients With Severe Pandemic Influenza A (H1N1) 2009 Virus Infection. Clinical Infectious Diseases, 2011; 52(4): 447–456. https://doi.org/10.1093/cid/ciq106
48. Huttunen, R., Heikkinen, T., & Syrjänen, J. Smoking and the outcome of infection. Journal of Internal Medicine, 2011; 269(3): 258–269. https://doi.org/10.1111/j.1365-2796.2010.02332.x
49. Information of Avigan Tablet in relation to Covid-19 | FUJIFILM Toyama Chemical Co., Ltd. (n.d.). Retrieved October 16, 2021. from https://www.fujifilm.com/fftc/en/avigan
50. Jacob H. Rand, Xiao-Xuan Wu,Anthony S. Quinn,Anthony W. Ashton,Pojen P. Chen, James J. Hathcock, Harry A. M. Andree, Douglas J. Taatjes. Hydroxychloroquine protects the annexin A5 anticoagulant shield from disruption by antiphospholipid antibodies: evidence for a novel effect for an old antimalarial drug. Blood, 2010; 115(11): 2292–2299. https://doi.org/10.1182/BLOOD-2009-04-213520
51. Joshi, S., Parkar, J., Ansari, A., Vora, A., Talwar, D., Tiwaskar, M., Patil, S., & Barkate, H. Role of favipiravir in the treatment of COVID-19. International Journal of Infectious Diseases, 2021; 102: 501–508. https://doi.org/10.1016/J.IJID.2020.10.069
52. Kalia, S., & Dutz, J. P. New concepts in antimalarial use and mode of action in dermatology. Dermatologic Therapy, 2007; 20(4): 160–174. https://doi.org/10.1111/J.1529-8019.2007.00131.X
53. Kanoh, S., & Rubin, B. K. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. Clinical Microbiology Reviews, 2010; 23(3): 590–615. https://doi.org/10.1128/CMR.00078-09
54. Koopmann, A., Georgiadou, E., Kiefer, F., & Hillemacher, T. Did the General Population in Germany Drink More Alcohol during the COVID-19 Pandemic Lockdown? Alcohol and Alcoholism, 2020; 55(6): 698–699. https://doi.org/10.1093/alcalc/agaa058
55. Lai et al. (2020): Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., & Hsueh, P. R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. International Journal of Antimicrobial Agents, 2020; 55(3): 105924. https://doi.org/10.1016/j.ijantimicag.2020.105924.
56. Legha, R. K., Moore, L., Ling, R., Novins, D., & Shore, J. Telepsychiatry in an Alaska Native Residential Substance Abuse Treatment Program. Telemedicine and E-Health, 2020; 26(7): 905–911. https://doi.org/10.1089/tmj.2019.0131

57. Li et al. (2020): Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. New England Journal of Medicine, 2020; 382(13): 1199–1207. https://doi.org/10.1056/NEJMoa2001316.
58. Lippi, G., & Henry, B. M. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). European Journal of Internal Medicine, 2020; 75: 107–108. https://doi.org/10.1016/j.ejim.2020.03.014
59. Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W., & Wang, M. (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discovery, 2020; 6(1): 1–4. https://doi.org/10.1038/s41421-020-0156-0
60. Lo, E., & Lasnier, B. Active smoking and severity of coronavirus disease 2019 (COVID-19): The use of significance testing leads to an erroneous conclusion. European Journal of Internal Medicine, 2020; 77: 125–126. https://doi.org/10.1016/j.ejim.2020.05.003
61. Lv, Z., Chu, Y., & Wang, Y. HIV protease inhibitors: a review of molecular selectivity and toxicity. HIV/AIDS - Research and Palliative Care, 2015; 7: 95–104. https://doi.org/10.2147/HIV.S79956
62. Mair-Jenkins, J., Saavedra-Campos, M., Baillie, K., Cleary, P., Khaw, F.-M., Shen Lim, W., Makki, S., Rooney, K. D., Nguyen-Van-Tam, J. S., & Beck, C. R. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral aetiology: a systematic review and exploratory meta-analysis. In Journal of Infectious Diseases Advance Access, 2014. http://jid.oxfordjournals.org/
63. Matos, C. P., Boléo-Tomé, J. P., Rosa, P., & Morais, A. Tobacco and COVID-19: A position from Sociedade Portuguesa de Pneumologia. Pulmonology, 2021; 27(2): 91–93. https://doi.org/10.1016/j.pulmoe.2020.11.002
64. Melamed, O. C., Hauck, T. S., Buckley, L., Selby, P., & Mulsant, B. H. COVID-19 and persons with substance use disorders: Inequities and mitigation strategies. Substance Abuse, 2020; 41(3): 286–291. https://doi.org/10.1080/08897077.2020.1784363
65. Miranda, S., Billoir, P., Damian, L., Thiebaut, P. A., Schapman, D., Besnerais, M. L., Jouen, F., Galas, L., Levesque, H., Cam-Duchez, V. L., Joannides, R., Richard, V., & Benhamou, Y. Hydroxychloroquine reverses the prothrombotic state in a mouse model of antiphospholipid syndrome: Role of reduced inflammation and endothelial dysfunction. PLOS ONE, 2019; 14(3): e0212614. https://doi.org/10.1371/journal.pone.0212614
66. Muriuki, J. M., & Atkinson, S. H. How eliminating malaria may also prevent iron deficiency in African children. Pharmaceuticals, 2018; 11(4). https://doi.org/10.3390/PH11040096
67. Nolan, D., Reiss, P., & Mallal, S. Adverse effects of antiretroviral therapy for HIV infection: a review of selected topics. Http://Dx.Doi.Org/10.1517/14740338.4.2.201, 2005; 4(2): 201–218. https://doi.org/10.1517/14740338.4.2.201
68. Nujić, K., Banjanac, M., Munić, V., Polančec, D., & Eraković Haber, V. Impairment of lysosomal functions by azithromycin and chloroquine contributes to anti-inflammatory phenotype. Cellular Immunology, 2012; 279(1): 78-86. https://doi.org/10.1016/j.cellimm.2012.09.007
69. Oliveira, K. R. H. M., dos Anjos, L. M., Araújo, A. P. S., Luz, W. L., Kauffmann, N., Braga, D. V., da Conceição Fonseca Passos, A., de Moraes, S. A. S., de Jesus Oliveira Batista, E., & Herculano, A. M. Ascorbic acid prevents chloroquine-induced toxicity in inner glial cells. Toxicology in Vitro, 2019; 56: 150–155. https://doi.org/10.1016/J.TIV.2019.01.008
70. Pandey, S., & Vyas, G. N. Adverse effects of plasma transfusion. Transfusion, 2012; 52(SUPPL. 1). https://doi.org/10.1111/j.1537-2995.2012.03663.x
71. Parnham, M. J., Haber, V. E., Giamarellos-Bourboulis, E. J., Perletti, G., Verleden, G. M., & Vos, R. Azithromycin: Mechanisms of action and their relevance for clinical applications. Pharmacology & Therapeutics, 2014; 143(2): 225-245. https://doi.org/10.1016/j.pharmthera.2014.03.003
72. Patanavanich, R., & Glantz, S. A. Smoking Is Associated With COVID-19 Progression: A Meta-analysis. Nicotine & Tobacco Research, 2020; 22(9): 1653–1656. https://doi.org/10.1093/ntr/ntaa082
73. Percha B, Altman RB. Informatics confronts drug-drug interactions. Trends Pharmacol Sci., 2013 Mar; 34(3): 178-84. doi: 10.1016/j.tips.2013.01.006. Epub 2013 Feb 13. PMID: 23414686; PMCID: PMC3808975.
74. Pigaiani, Y., Zoccante, L., Zocca, A., Arzenton, A., Menegolli, M., Fadel, S., Ruggeri, M., & Colizzi, M. Adolescent Lifestyle Behaviors, Coping Strategies and Subjective Wellbeing during the COVID-19 Pandemic: An Online Student Survey. Healthcare, 2020; 8(4): 472. https://doi.org/10.3390/healthcare8040472
75. Plantone, D., & Koudriavtseva, T. Current and Future Use of Chloroquine and Hydroxychloroquine in Infectious, Immune, Neoplastic, and Neurological Diseases: A Mini-Review. Clinical Drug Investigation, 2018; 38(8): 653–671. https://doi.org/10.1007/S40261-018-0656-Y
76. Pollard, M. S., Tucker, J. S., & Green, H. D. Changes in Adult Alcohol Use and Consequences During the COVID-19 Pandemic in the US. JAMA Network Open, 2020; 3(9): e2022942. https://doi.org/10.1001/jamanetworkopen.2020.22942
77. Porto, G., Cruz, E., Teles, M. J., & De Sousa, M. HFE Related Hemochromatosis: Uncovering the

Inextricable Link between Iron Homeostasis and the Immunological System. Pharmaceuticals, 2019; 12(3): 122. https://doi.org/10.3390/ph12030122
78. Quiros Roldan, E., Biasiotto, G., Magro, P., & Zanella, I. The possible mechanisms of action of 4-aminoquinolines (chloroquine/hydroxychloroquine) against Sars-Cov-2 infection (COVID-19): A role for iron homeostasis? Pharmacological Research, 2020; 158: 104904. https://doi.org/10.1016/J.PHRS.2020.104904
79. Rainsford, K. D., Parke, A. L., Clifford-Rashotte, M., & Kean, W. F. (2015). Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology, 2015; 23(5): 231–269. https://doi.org/10.1007/S10787-015-0239-Y
80. Ramalho, R. Alcohol consumption and alcohol-related problems during the COVID-19 pandemic: a narrative review. Australasian Psychiatry, 2020; 28(5): 524–526. https://doi.org/10.1177/1039856220943024
81. Rasmussen, S. A., Jamieson, D. J., & Uyeki, T. M. Effects of influenza on pregnant women and infants. In American Journal of Obstetrics and Gynecology, 2012; 207(3). Mosby Inc. https://doi.org/10.1016/j.ajog.2012.06.068
82. Reddy, R. K., Charles, W. N., Sklavounos, A., Dutt, A., Seed, P. T., & Khajuria, A. The effect of smoking on COVID-19 severity: A systematic review and meta-analysis. Journal of Medical Virology, 2021; 93(2): 1045–1056. https://doi.org/10.1002/jmv.26389
83. Rehm, J., Kilian, C., Ferreira-Borges, C., Jernigan, D., Monteiro, M., Parry, C. D. H., Sanchez, Z. M., & Manthey, J. Alcohol use in times of the <scp>COVID</scp> 19: Implications for monitoring and policy. Drug and Alcohol Review, 2020; 39(4): 301–304. https://doi.org/10.1111/dar.13074
84. Roldan, E. Q., Biasiotto, G., Magro, P., & Zanella, I. The possible mechanisms of action of 4-aminoquinolines (chloroquine/hydroxychloroquine) against Sars-Cov-2 infection (COVID-19): A role for iron homeostasis? Pharmacological Research, 2020; 158: 104904. https://doi.org/10.1016/J.PHRS.2020.104904
85. Rossignol (2014): Rossignol, J.-F. Nitazoxanide: A broad-spectrum antiviral agent that is being developed for the treatment of COVID-19. Journal of Infection, 2014; 68(3): 238-239. https://doi.org/10.1016/j.jinf.2014.11.001.
86. Rossignol (2016): Rossignol, J.-F. Nitazoxanide: A first-in-class broad-spectrum antiviral agent. Antiviral Research, 2016; 139: 1-4. https://doi.org/10.1016/j.antiviral.2016.02.010.
87. Ruan et al. (2020): Ruan, Q., Yang, K., Wang, W., Jiang, L., & Song, J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine, 2020; 46(5): 846–848. https://doi.org/10.1007/s00134-020-05991-x.
88. Schoeman, D., & Fielding, B. C. Coronavirus envelope protein: Current knowledge. Virology Journal, 2019; 16(1). https://doi.org/10.1186/S12985-019-1182-0
89. Shannon, A., Selisko, B., Le, N., Huchting, J., Touret, F., Piorkowski, G., & al., et. Favipiravir strikes the SARS-CoV-2 at its Achilles heel, the RNA polymerase. BioRxiv, 2020. https://doi.org/10.1101/2020.05.15.098731
90. Sheahan, T. P., Sims, A. C., Leist, S. R., Schäfer, A., Won, J., Brown, A. J., Montgomery, S. A., Hogg, A., Babusis, D., Clarke, M. O., Spahn, J. E., Bauer, L., Sellers, S., Porter, D., Feng, J. Y., Cihlar, T., Jordan, R., Denison, M. R., & Baric, R. S. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature Communications, 2020; 11(1): 1-14. https://doi.org/10.1038/s41467-019-13940-6
91. Shen, C., Wang, Z., Zhao, F., Yang, Y., Li, J., Yuan, J., Wang, F., Li, D., Yang, M., Xing, L., Wei, J., Xiao, H., Yang, Y., Qu, J., Qing, L., Chen, L., Xu, Z., Peng, L., Li, Y., … Liu, L. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA, 2020a; 323(16): 1582–1589. https://doi.org/10.1001/JAMA.2020.4783
92. Shen, C., Wang, Z., Zhao, F., Yang, Y., Li, J., Yuan, J., Wang, F., Li, D., Yang, M., Xing, L., Wei, J., Xiao, H., Yang, Y., Qu, J., Qing, L., Chen, L., Xu, Z., Peng, L., Li, Y., … Liu, L. Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma. JAMA - Journal of the American Medical Association, 2020b; 323(16): 1582–1589. https://doi.org/10.1001/jama.2020.4783
93. Simou, E., Britton, J., & Leonardi-Bee, J. Alcohol and the risk of pneumonia: a systematic review and meta-analysis. BMJ Open, 2018; 8(8): e022344. https://doi.org/10.1136/bmjopen-2018-022344
94. Sulkowski, M. S., Thomas, D. L., Chaisson, R. E., & Moore, R. D. Hepatotoxicity Associated With Antiretroviral Therapy in Adults Infected With Human Immunodeficiency Virus and the Role of Hepatitis C or B Virus Infection. JAMA, 2000; 283(1): 74–80. https://doi.org/10.1001/JAMA.283.1.74
95. Testino, G., Matone, A., Ghirini, S., Pellicano, R., Caputo, F., Scafato, E., & Executive Committee of the Italian Society on Alcohol (SIA). Thrombosis following Covid-19 vaccination: a possible role of alcohol consumption? A suggestion from the Italian Society on Alcohol. Minerva Medica., 2021a. https://doi.org/10.23736/S0026-4806.21.07670-9
96. Testino, G., Vignoli, T., Patussi, V., Allosio, P., Amendola, M. F., Aricò, S., Baselice, A., Balbinot, P., Campanile, V., Fanucchi, T., Macciò, L., Meneguzzi, C., Mioni, D., Parisi, M., Renzetti, D., Rossin, R., Gandin, C., Bottaro, L. C., Caio, G., …

Caputo, F. (2021b Gao, Q. Y., Chen, Y. X., & Fang, J. Y. 2019 Novel coronavirus infection and gastrointestinal tract. Journal of Digestive Diseases, 2020; 21(3): 125–126. https://doi.org/10.1111/1751-2980.12851

97. Tingbo: Handbook of COVID-19 Prevention and Treatment... - Google Scholar. (n.d.). Retrieved October 15, 2021. from https://scholar.google.com/scholar_lookup?title=Handbook%20of%20COVID-19%20Prevention%20and%20Treatment%2C%20Handbook%20of%20Covid-19%2C%20Prevention%20and%20Treatment.%20The%20First%20Affiliated%20Hospital&author=L.%20Tingbo&publication_year=2020
98. Touret, F., & de Lamballerie, X. Of chloroquine and COVID-19. Antiviral Research, 2020; 177: 104762. https://doi.org/10.1016/J.ANTIVIRAL.2020.104762
99. Ullberg, S., Lindquist, N. G., & S van den Broek, M. P. H., Möhlmann, J. E., Abeln, B. G. S., Liebregts, M., van Dijk, V. F., & van de Garde, E. M. W. 2020 Chloroquine-induced QTc prolongation in COVID-19 patients. Netherlands Heart Journal, 2020; 28(7): 28(7): 406–409. https://doi.org/10.1007/S12471-020-01429-7
100. Ulrich, H., Pillat, M.M. CD147 as a Target for COVID-19 Treatment: Suggested Effects of Azithromycin and Stem Cell Engagement. Stem Cell Rev and Rep., 2020; 16: 434–440. https://doi.org/10.1007/s12015-020-09976-7
101. Urbanski, G., Caillon, A., Poli, C., Kauffenstein, G., Begorre, M. A., Loufrani, L., Henrion, D., & Belizna, C. Hydroxychloroquine partially prevents endothelial dysfunction induced by anti-beta-2-GPI antibodies in an in vivo mouse model of antiphospholipid syndrome. PLoS ONE, 2018; 13(11). https://doi.org/10.1371/JOURNAL.PONE.0206814
102. Usman, M. S., Siddiqi, T. J., Khan, M. S., Patel, U. K., Shahid, I., Ahmed, J., Kalra, A., & Michos, E. D. Is there a smoker's paradox in COVID-19? BMJ Evidence-Based Medicine, 0, bmjebm, 2020; 111492. https://doi.org/10.1136/bmjebm-2020-111492
103. Uzunova, K., Filipova, E., Pavlova, V., & Vekov, T. Insights into antiviral mechanisms of remdesivir, lopinavir/ritonavir and chloroquine/hydroxychloroquine affecting the new SARS-CoV-2. Biomedicine & Pharmacotherapy, 2020; 131: 110668. https://doi.org/10.1016/J.BIOPHA.2020.110668
104. van den Broek, M. P. H., Möhlmann, J. E., Abeln, B. G. S., Liebregts, M., van Dijk, V. F., & van de Garde, E. M. W. (2020). Chloroquine-induced QTc prolongation in COVID-19 patients. Netherlands Heart Journal, 2020; 28(7): 406–409. https://doi.org/10.1007/S12471-020-01429-7
105. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, Seidah NG, Nichol ST. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J., 2005 Aug 22; 2: 69. doi: 10.1186/1743-422X-2-69. PMID: 16115318; PMCID: PMC1232869..
106. Wang et al. (2020a): Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. The Lancet, 2020; 395(10236): 1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9.
107. Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., & Xiao, G. (2020b). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research, 2020; 30(3): 269–271. https://doi.org/10.1038/s41422-020-0282-0
108. Wang, M., Shu, B., Bai, W.-X., Liu, J., Yao, J., Pan, W.-N., & Pan, Y.-Y. A 4-week oral toxicity study of an antiviral drug combination consisting of arbidol and acetaminophen in rats. Http://Dx.Doi.Org/10.3109/01480540903311050, 2010; 33(3): 244–253. https://doi.org/10.3109/01480540903311050
109. WHO: WHO R&D blueprint–ad-hoc expert consultation... - Google Scholar. (n.d.). Retrieved October 15, 2021. from https://scholar.google.com/scholar_lookup?title=WHO%20R%26D%20Blueprint%20%E2%80%93%20Ad-Hoc%20Expert%20Consultation%20on%20Clinical%20Trials%20for%20Ebola%20Therapeutics&author=WHO&publication_year=2018
110. Wulan, W. N., Heydet, D., Walker, E. J., Gahan, M. E., & Ghildyal, R. Nucleocytoplasmic transport of nucleocapsid proteins of enveloped RNA viruses. Frontiers in Microbiology, 2015; 6(JUN). https://doi.org/10.3389/fmicb.2015.00553
111. Xu et al. (2020): Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine, 2020; 8(4): 420–422. https://doi.org/10.1016/S2213-2600(20)30076-X.
112. Yang et al. Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., et al. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. The Lancet Respiratory Medicine, 2020; 8(5): 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5.
113. Yang, J., Yang, X., Yang, J., & Li, M. Hydroxychloroquine inhibits the differentiation of Th17 cells in systemic lupus erythematosus. Journal of Rheumatology, 2018; 45(6): 818–826. https://doi.org/10.3899/JRHEUM.170737
114. Yang, Xueqing & Blagodatsky, Sergey & Lippe, Melvin & Liu, Feng & Hammond, Jim & Xu, Jianchu & Cadisch, Georg. Yang et al, 2016.
115. Ye, Q., Wang, B., & Mao, J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19.

Journal of Infection, 2020; 80(6): 607–613. https://doi.org/10.1016/j.jinf.2020.03.037

116. Yusuf, I. H., Foot, B., Galloway, J., Ardern-Jones, M. R., Watson, S.-L., Yelf, C., Burdon, M. A., Bishop, P. N., & Lotery, A. J. The Royal College of Ophthalmologists recommendations on screening for hydroxychloroquine and chloroquine users in the United Kingdom: executive summary. Eye, 2018; 32(7): 1168–1173. https://doi.org/10.1038/s41433-018-0136-x
117. Zelman, S., Holzwanger, E., Malik, R., & Dickstein, A. Alcoholic Hepatitis and COVID-19: The Question of Steroids. ACG Case Reports Journal, 2020; 7(12): e00504. https://doi.org/10.14309/crj.0000000000000504
118. Zeng et al. Zeng, J. H., Liu, Y. X., Yuan, J., Wang, F. X., Wu, W. B., Li, J. X., et al. (2020). First case of COVID-19 complicated with fulminant myocarditis: A case report and insights. Infection, 2020; 48(5): 773–777. https://doi.org/10.1007/s15010-020-01424-5.
119. Zhang, B., Liu, S., Tan, T., Huang, W., Dong, Y., Chen, L., Chen, Q., Zhang, L., Zhong, Q., Zhang, X., Zou, Y., & Zhang, S. Treatment With Convalescent Plasma for Critically Ill Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. Chest, 2020; 158(1): e9–e13. https://doi.org/10.1016/j.chest.2020.03.039
120. Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K., & Hilgenfeld, R., 2020. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science. https://doi.org/abb3405
121. Zheng et al. Zheng, Y. Y., Ma, Y. T., Zhang, J. Y., & Xie, X. (2020). COVID-19 and the cardiovascular system. Nature Reviews Cardiology, 2020; 17(5): 259–260. https://doi.org/10.1038/s41569-020-0360-5.
122. Zhonghua et al. Zhonghua, L., Zhendong, Z., & Lixia, Z. (2020). The efficacy and safety of chloroquine for the treatment of COVID-19. Journal of Zhejiang University (Medical Sciences), 2020; 49(2): 234-239. https://doi.org/10.3785/j.issn.1008-9292.2020.02.02.
123. Zhou, B., Zhong, N., & Guan, Y. Treatment with Convalescent Plasma for Influenza A (H5N1) Infection. New England Journal of Medicine, 2007; 357(14): 1450–1451. https://doi.org/10.1056/NEJMc070359