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Pathogenesis of SARS-CoV-2 and Important Insights on its Potent Inhibitors Remdesivir and Chloroquine - A Review

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A B S T R A C T

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is enveloped, single-stranded, positive- sense RNA virus which is responsible for coronavirus disease 2019 (COVID-19) characterized by pulmonary infection in humans. Effective prophylactic and therapeutic management for COVID-19 are urgently required to control this pandemic. Angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV-2 in host cell. Spike protein of virus bindswith the peptidase domain of ACE2 receptor. After binding with the receptor the next step of virus is to gain entry to the host cell cytosol which is accomplished by the proteolyti cleavage of S protein in acidic pH. The proteolytic cleavage is followed by fusion of SARS-CoV-2 and its host cell membrane leading to release of the viral genomeinto the cytoplasm. The anti-malarialdrug chloroquine and its analog hydroxy-chloroquine are known to restrict viral replication by increasing endosomal pH which inhibits viral-cell fusion. After uncoating, viral RNA genome is translated to form structural viral protein with the help of RNA-dependent RNA polymerase (RdRp), which is the target for adenosine analogue remdesivir. The combination therapy including Remdesivir and chloroquine are exceptionally successful in the control of 2019-nCoV disease in vitro. Fundamental preliminaries of Remdesivir and chloroquine repurposing in the treatment of COVID-19 have been empowering, prompting a few new trials. In this review, pathogenesis of the SARS-CoV-2 and the potential mechanism of two potent inhibitors remdesivir and chloroquine as effective therapeutic agents against COVID-19 are described.

Introduction

The novel Corona Virus Disease 2019 (COVID-19) is a global pandemic which emerged in Wuhan City of China in December 2019, and currently affected more than 200 countries while posing a high threat owing to rapidly increasing number of cases and deaths on daily basis (Chan *et al.*, 2020; Chatterjee *et al.*, 2020; Marty and Jones, 2020; WHO, 2020). Coronaviruses belongs to *betacoronavirus* (β-CoVs or Beta-CoVs) genus (Zhou *et al.*, 2020), family Coronaviridae, of enveloped, single-stranded, positive-strand non-segmented RNA viruses. The name "coronavirus," was coined in 1968, which means crown-like morphology which was seen in the electron microscope (Tyrrel,

1968). The clinical sign is that of a respiratory disease with a manifestation ranging from a mild cold-like sickness, to an extreme viral pneumonia prompting intense respiratory trouble disorder that is potentially fatal. Clinical preliminaries and in-depth examinations to study the infection pathogenesis, its origin starting point and gaining transmission and spread to humans, and how it influences people are progressing. Contrasted with SARS-CoV and MERS-CoV, COVID-19 infection displays quicker human-to-human transmission, hence prompting WHO to assertion of an overall general well-being crisis (Chan *et al.,* 2020).

Since, COVID-19 is spreading like havoc in form of pandemic across the countries, prompt prophylactic and therapeutic measures are required. The development of new drugs and vaccines demands sufficient time for production, pre-clinical, clinical trials, manufacturing and validation, therefore to meet the requirement repurposing of drugs is a smart strategy and need of the current situation.

With the help of knowledge of SARS-CoV-2 virus architecture and pathogenesis, target sites can be identified for proposing drugs which can impose anti-viral activity with pronounced safety and efficacy (Garcia-Serradilla *et al.,* 2019; Rosa and Santos, 2020).

Although, specifically efficacious drugs against the SARS-CoV-2 are yet to be established the chloroquine and hydroxychloroquine have been considered as a potential therapeutic option to treat COVID-19. The chloroquine phosphate is reported to be the first drug to display efficacy against SARS-CoV-2 in China (Gao *et al.,* 2020). Due to easy availability and low cost of the chloroquine and hydroxychloroquine these drugs may prove crucial to curb the ongoing pandemic after proper evaluation of its efficacy and safety by clinical trials. A nucleotide analog viz. remdesivir which was reported to be administered in Ebola virus patients has also proven effective against coronavirus (Costanzo *et al.,* 2020). The present article describes the pathogenesis of SARS-CoV-2 and gives insights on its two potent inhibitors Remdesivir and Chloroquine for use as effective drugs against COVID-19.

Pathogenesis of SARS-CoV-2

SARS-CoV-2 virus has three envelope proteins which help the virus to enter into the host cell viz the spike (S) protein, the envelope (E) protein and the membrane (M) protein. Beside this virus also have nucleocapsid (N) which is an important element of the replicase complex. First interaction of virus to the host cell is started by associations between the S protein and its receptor.

On account of SARS-CoV, the spike glycoprotein (S protein) on the SARS-CoV-2 surface recognizes receptor and mediates viral and host cell membrane fusion (Gallagher *et al.,* 2001; Simmons *et al.,* 2013). When virus attacks, the trimeric structured S protein is cleaved into S1 and S2 subunits.

S2 subunit is responsible for the post fusion conformation (Simmons *et al.,* 2013; Song *et al.,* 2018). S1 subunit has the region for receptor binding, which straight forwardly binds with the angiotensin-converting enzyme 2 (ACE2) at its peptidase domain (PD) (Li *et al.,* 2005), while S2 is liable for fusion of membranes. When S1 subunit binds with ACE2 receptor on the host surface another cleavage site S2 is uncovered and is targeted by host proteases, a procedure which is important for viral spreading (Millet *et al.,* 2015; Simmons *et al.,* 2005). The S protein-receptor binding is the prime step of

coronavirus to infect a host. The receptor used by SARS-CoV-2 to enter the host is ACE-2 (Li *et al.,* 2003). The next step of virus is to gain entry to the host cell cytosol. This is accomplished by the proteolytic cleavage of S protein by cathepsin, TMPRRS2 or any other protease requires acidic environment for the cleavage that is not possible under physiological pH. The proteolytic cleavage is followed by fusion of SARS-CoV-2 and its host cell membrane leading to release of the viral genome into the cytoplasm (Bosch *et al.,* 2003). Following uncoating, the positive sense RNA genome is released which is translated to large polyprotein that experiences proteolytic processing to form a RNA-dependent RNA polymerase.

Through the activity of the RNA polymerase, a full-length, antisense negative-strand template is formed. The subgenomic negative sense templates give rise to subgenomic negative-sense mRNAs which are further translated to form structural viral proteins. Following replication, the envelope proteins are translated and embedded into the endoplasmic reticulum and afterward move to the Golgi compartment. Viral genomic RNA is bundled into the nucleocapsid and afterward envelope proteins are integrated to form mature virions. The M protein, which restricts to the trans-Golgi network, assumes a fundamental job during viral assembly by associating with different proteins of the virus. Following assembly, the viruses are carried to the cell surface within vesicles and are discharged by exocytosis (Devaux *et al.,* 2020). The discharged virus can infect different cells and replicate inside the parent cell through binding to CEACAM-1 (Bergmann *et al.,* 2006; Shereen *et al.,* 2020). These viral particles reach to bronchi, alveoli, and extrapulmonary organs, and causes pneumonia which are the main cause for death.

Remdesivir and chloroquine as potent inhibitors of SARS-CoV-2

Remdesivir

The RNA dependent RNA polymerase also called as Nsp12 plays an important role in the replication and transcription of SARS-CoV-2. Therefore, Nsp12 is viewed as a key target for antiviral inhibitors. The drug targeting RNA-dependent RNA polymerase (RdRp) of SARS-CoV could be effective in treatment with SAR-CoV-2 because SARS-CoV-1 have 82% RNA sequence resemblance, and 96% sequence resemblance of RdRp with SARS-CoV-2 (Liu *et al.,* 2020) (Figure 1).

Remdesivir, a wide acting anti-viral drug molecule could likely be beneficial for the treatment of COVID-19 (Wang *et al.,* 2020; Holshue *et al.,* 2019; Rabaan *et al.,* 2020). Remdesivir is a 2-ethylbutyl L-alaninate phosphoramidateprodrug (Warren *et al.,* 2016) that has wide antiviral property against various families of virus *in vitro* (Lo *et al.,* 2017), including the respiratory syncytial virus, Hendra virus, Ebola and Nipah virus in non-human primate models (Warren *et al.,* 2016; Singh *et al.,* 2018; Lo *et al.,* 2019). Remdesivir (referred with code GS-5734™) is as adenosine analog, prodrugof an adenosine C–nucleoside (Ko *et al.,* 2020). More precisely, remdesivir (GS-5734) is phosphorylated from GS-441524 (Amirian and Levy, 2020) and is 3-30 times more active than GS-441524 (Menachery *et al.,* 2015). Studies have shown that remdesivir inhibit replication of MERS-CoV and SARS-CoV and has also proved it efficacy in pre-pandemic Bat-CoVs, and human-CoV virus in epithelial cells of airway in human which indicates that remdesivir likewise could hinder the replication of a wide range of coronaviruses (Sheahan *et al.,* 2017; Al-Tawfiq *et al.,* 2020).

Remdesivir, an adenosine analogue, works after the entry of the virus into the host cell. After entering the host cell it get metabolized into nucleoside triphosphate (NTP) which competes with ATP and lowers the replication of human as well as in zoonotic delta coronaviruses by inhibiting replication of RNA (Brown *et al.*, 2019). It gets integrated in the viral RNA chains and results in RNA chain termination. This implies that the viral RNA dependent RNA polymerase introduces adenosine analog rather than the natural nucleotide (Agostini *et al.*, 2018). It adds three additional nucleotides and afterward stops due to pre-mature termination of RNA replication, as viral exonucleases does not work properly and due to faulty proof reading of nucleotide chain, replication of viral RNA could not be completed (Agostini *et al.*, 2018). As a result, the virus can't replicate its genome; it cannot reproduce and make its host diseased. The researchers hypothesize that the additional three nucleotides may shield the drug from being expelled by the coronavirus' exonuclease enzyme (Gordon *et al.*, 2020).

Due to beneficial anti-viral effects remdesivir has also been tried along with interferon beta and have demonstrated promising, protective and safe effects against MERS-CoV in murine model (Cao, 2020). In pre-clinical studies the broad-spectrum anti coronavirus activity of remdesivir was demonstrated and for evaluation of safety and efficacy of remdesivir in hospitalized patients with mild to moderate COVID-19 a randomized, controlled, double blind clinical trial has already been designed (Cao, 2020).*In vitro* and *in vivo* both studies have confirmed favourable effects of remdesivir on animal models like transgenic mice and rhesus macaques against MERS-CoV (Amirian and Levy, 2020; de Wit *et al.*, 2020). Remdesivir is presently being tried in five COVID-19 clinical preliminaries that have been set up very fast. A fundamental report on COVID-19 patients treated with the trial of remdesivir recommends that the antiviral drug may bring down the danger of death in seriously sick patients and improve the state of patients depending on breathing devices. Although, clinical impacts of remdesivir on COVID-19 patients are unknown the scientists are putting their best possible step forward and waiting patiently for the final results of ongoing clinical trials.

Chloroquine

Another widely used medication to treat SAR-CoV-2 is Chloroquine, as approved by the US Food and Drug Administration (FDA) despite lack of full evidence of its action and a few side effects as well (Devaux *et al.*, 2020; Gao and Hu, 2020). It is a notable anti-malarial drug and immunomodulator which has been accounted as a potential broad spectrum antiviral medication (Savarino *et al.*, 2006; Yan *et al.*, 2013). The antiviral property of chloroquine and its derivatives against RNA viruses was earlier reported for SARS-CoV-1, rabies virus; influenza virus; Nipah virus; Chikungunya virus; polio virus and for many more (Devaux *et al.*, 2020).

Chloroquine phosphate is now an approved drug compound possessing anti-SARS-CoV-2 activity and hence is recommended to be used against COVID-19 but under clinical supervision (Duan *et al.*, 2020). Chloroquine and/or hydroxychloroquine any compound can be used, however hydroxychloroquine is recommended over chloroquine due to rapid GI absorption, reduced toxic effects, and wider safety spectrum, which can even be administered safely in pregnant patients (Liu *et al.*, 2020). Moreover, hydroxychloroquine is a chloroquine analog considered as an immunomodulator and reported to have more potent *in vitro* inhibitory effect on SARS-CoV-2 than chloroquine (Yao *et al.*, 2020;

Zhou *et al.,* 2020). The difference between chloroquine and hydroxychloroquine is that the N-ethyl substituent in chloroquine is β-hydroxylated in hydroxychloroquine (Devaux *et al.,* 2020). In treatment regimen of hydroxyl-chloroquine, loading dose should be followed by maintenance dosage (Colson *et al.,* 2020). Administration of hydroxyl-chloroquine depicted marked reduction in occurrence of serious fatal clinical symptoms of COVID-19 (Yao *et al.,* 2020; Zhou *et al.,* 2020). Chloroquine (CQ) is a 4-aminoquinolone derivative which is a weak base and can enter the cells and accumulate in endosomes, trans-Golgi network vesicles or lysosomes like acidic compartments raising cell pH (Thome *et al.,* 2013). Chloroquine is known to inhibit viral infection by increasing endosomal pH i.e making it alkaline and thus inhibiting endocytosis and viral-cell fusion which require acidic pH. By altering the pH, chloroquine also affects the post-translational modification of viral proteins (Devaux *et al.,* 2020). It blocks the action of pH dependent enzymes like glycosyltransferases or proteases in golgi network which impedes the maturation of viral protein (García-Serradilla *et al.,* 2019). It interferes with the M protein maturation which in turn effect the virion assembly and replication (Randolph *et al.,* 1990). It also affects the glycosylation of ACE2 cell receptors of SARS-CoV. Other than its antiviral action, chloroquine is a known drug for autoimmune disease, which may also synergistically improve its antiviral impact *in vivo*. The SARS-CoV-2 affected patient's shows increase in cytokines such as interleukins and other inflammatory agent which causes cell apoptosis, as well as a cytokine storm.

Chloroquine is known to alter these cytokine which can cause havoc in the body and thus helps in body defence. Chloroquine was reported to have an inhibitory effect on the production and release of cytokines like IL-6 and TNFα and may prove crucial in suppression of the COVID-19 associated cytokine storm (Gao, *et al.,* 2020). Hydroxychloroquine suppresses the activity of T-cells to regulate the cytokine storm in the body. Chloroquine affects the immune system not only by regulating the cytokines but also via affecting MAPK signaling pathways in THP-1 cells and caspase-1 (Steiz *et al.,* 2003). The MAPK signaling is required by the virus for its replication (Briant *et al.,* 1998). Beside attachment of SAR-CoV-2 with protein membrane receptor, the virions can also bind with the gangliosides and sialic acid containing glycoprotein in the respiratory tract (Matrosovich *et al.,* 2015). Chloroquine has higher binding affinity with these receptor in comparison with SARS-CoV-2, and thus prevent attachment of virus to the cells of pulmonary system to check the viral entry (Fantini *et al.,* 2020). The inhibitory impacts of chloroquine on virus can be before or after the virus entry thus proposing both its prophylactic and therapeutic role.

Recently a study hypothesized, consequential and synergistic action of hydroxychloroquine and ivermectin for chemoprophylaxis and clinical care of COVID-19 patients on simultaneous administration (Patrì and Fabbrocini, 2020). However, in a pilot study chloroquine was reported superior to lopinavir/ritonavir in decreasing the period of hospitalization and improving the pulmonary radiological appearance (Gao and Hu, 2020; Huang *et al.,* 2020). In addition, adverse effects reported to be associated with chloroquine includes nausea, vomiting, diarrhea, abdominal pain, rashes, itching, cough and shortness of breath (Gao and Hu, 2020; Huang *et al.,* 2020). The clinical study onhydroxychloroquine to treat COVID-19 revealed reduction in period of fever, decrease in the duration of cough and improvement in lung images suggesting the usefulness of the drug in management of COVID-19 (Chen *et al.,* 2020).

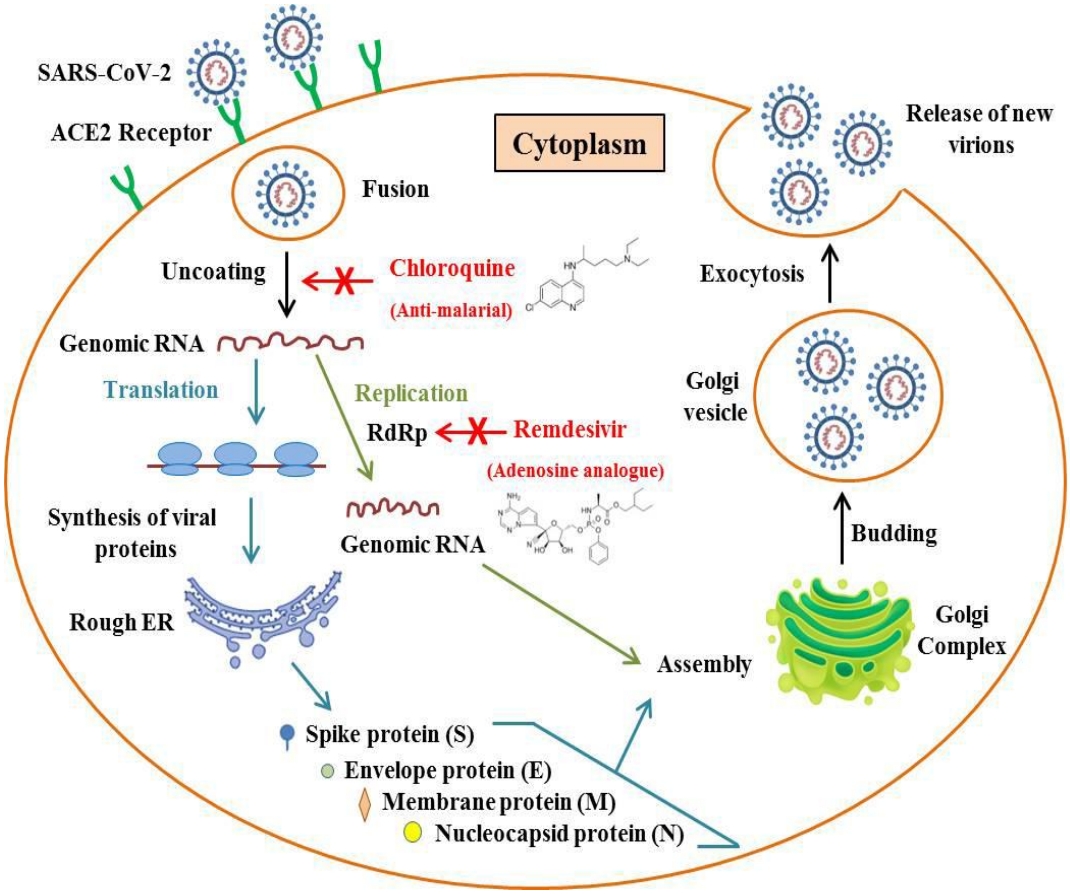

Figure.1 Life cycle of SARS-CoV-2 in host cells and point of targets for Remdesivir and Chloroquine

Notwithstanding the notable elements of chloroquine, increasing the endosomal pH, the medication seems to affect with the terminal glycosylation of ACE2 cell receptor for SARS-CoV-2 (Gao *et al.*, 2020; Vincent *et al.*, 2005). This may adversely impact the virus-receptor binding and abrogate the infection, by the rise of vesicular pH, bringing about the hindrance in uncoating of virus (Figure 1) and spread of SARS-CoV-2 (Vincent *et al.*, 2005; Faiq *et al.*, 2020).

Chloroquine is generally effective, safe and cheap medication utilized for treating numerous human illnesses including malaria, human immunodeficiency virus and amoebiosis and is compelling in hindering the disease and spread of SARS-CoV-2 in cell culture. The clinical trial for chloroquine prophylactic and therapeutic effect against SARS-CoV-2 has started in United States.

Research performed in Central China's Hunan Province, South China's Guangdong Province and in Beijing hospital, China revealed that combined therapy of chloroquine and remdesivir effectively reduce the SARS-CoV-2 activity under *in vitro* conditions and they recommended use of this drug-combination for treating COVID-19 infected patients (Hu *et al.*, 2020). Chinese medical advisory board has proposed addition of chloroquine in the treatment prescribed for SARS-CoV-2 (Wang *et al.*, 2020).

The fast worldwide spread of COVID-19 infection has stressed the requirement for the advancement of new coronavirus immunizations and therapeutics. In this context, researchers already started exploring all possible remedies and combinations for containment of this pandemic. Many antivirals, protease inhibitors and supplementary pharmaceuticals were considered and used for treatment and chemoprophylaxis of earlier and ongoing coronavirus disease.

Although, no therapeutic agent provided promising result in case of ongoing pandemic but chloroquine and remdesivir were considered effective on the basis of many studies and *in vitro* trials. The viral polymerase RdRp looks a key target for new therapeutic remdesivir which is a nucleotide analog and prevents replication of viral genomic RNA. The ability of anti-malarial drug chloroquine and its analog hydroxyl-chloroquine to raise the endosomal pH and hence inhibiting the cell fusion and release of viral genome into the cytoplasm is also explored for containment of SARS-CoV-2 infection. The Chinese medical advisory board has also recommended the inclusion of chloroquine in the treatment prescribed for SARS-CoV-2 infection. Many *in vitro* studies suggested that remdesivir and chloroquine may prove highly useful and effective in the control of COVID-19 infection.

The combination therapy including chloroquine and remdesivir was found highly effective in reduction of the SARS-CoV-2 activity under in vitro conditions. In addition, this drug combination is recommended for the use in treatment of COVID-19 patients. The utilization of these drugs in human patients demonstrated their effectiveness against different ailments; we propose that they ought to be assessed in human patients experiencing the novel coronavirus illness.

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References

Agostini, M.L., Andres, E.L., Sims, A.C., Graham, R.L., Sheahan, T.P., Lu, X., Smith, E.C., Case, J.B., Feng, J.Y., Jordan, R. and Ray, A.S., 2018. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *MBio*, *9*(2), pp.e00221-18.

Al-Tawfiq, J.A., Al-Homoud, A.H. and Memish, Z.A., 2020. Remdesivir as a possible therapeutic option for the COVID-19. *Travel medicine and infectious disease*.Bergmann, C.C., Lane, T.E. and Stohlman, S.A., 2006. Coronavirus infection of the central nervous system: host–virus stand-off. *Nature Reviews Microbiology*, *4*(2), pp.121-132.

Bosch, B.J., van der Zee, R., de Haan, C.A. and Rottier, P.J., 2003. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. *Journal of virology*, *77*(16), pp.8801-8811.

Briant, L., Robert-Hebmann, V., Acquaviva, C., Pelchen-Matthews, A., Marsh, M. and Devaux, C., 1998. The protein tyrosine kinase p56 lck is required for triggering NF-κB activation upon interaction of human immunodeficiency virus type 1 envelope glycoprotein gp120 with cell surface CD4. *Journal of virology*, *72*(7), pp.6207-6214.

Brown, A.J., Won, J.J., Graham, R.L., Dinnon III, K.H., Sims, A.C., Feng, J.Y., Cihlar, T., Denison, M.R., Baric, R.S. and Sheahan, T.P., 2019. Broad spectrum

antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral research*, *169*, p.104541.

Cao B., 2020. Mild/moderate 2019-nCoV remdesivir RCT - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04252664. Accessed date: 13 February 2020.

Chan, J.F.W., Yuan, S., Kok, K.H., To, K.K.W., Chu, H., Yang, J., Xing, F., Liu, J., Yip, C.C.Y., Poon, R.W.S. and Tsoi, H.W., 2020. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *The Lancet*, *395*(10223), pp.514-523.

Chatterjee, P., Nagi, N., Agarwal, A., Das, B., Banerjee, S., Sarkar, S., Gupta, N. and Gangakhedkar, R.R., 2020. The 2019 novel coronavirus disease (COVID-19) pandemic: A review of the current evidence. *The Indian Journal of Medical Research*.

Chen, Z., Hu, J., Zhang, Z., Jiang, S., Han, S., Yan, D., Zhuang, R., Hu, B. and Zhang, Z., 2020. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *MedRxiv*.

Colson, P., Rolain, J.M., Lagier, J.C., Brouqui, P. and Raoult, D., 2020. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*, *105932*(10.1016).

Costanzo, M., De Giglio, M.A.R. and Roviello, G.N., 2020. SARS CoV-2: Recent Reports on Antiviral Therapies Based on Lopinavir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, Remdesivir, Favipiravir and Other Drugs for the Treatment of the New Coronavirus. *Current Medicinal Chemistry*.

Devaux, C.A., Rolain, J.M., Colson, P. and Raoult, D., 2020. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?.*International journal of antimicrobial agents*, p.105938.doi: 10.1016/j.ijantimicag.2020.105938.

de Wit, E., Feldmann, F., Cronin, J., Jordan, R., Okumura, A., Thomas, T., Scott, D., Cihlar, T., Feldmann, H., 2020. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *ProcNatlAcadSci U S A. 117(12)*:6771-6776. doi: 10.1073/pnas.1922083117.

Duan, Y.J., Liu, Q., Zhao, S.Q., Huang, F., Ren, L., Liu, L. and Zhou, Y.W., 2020. The Trial of Chloroquine in the Treatment of Corona Virus Disease 2019 (COVID-19) and Its Research Progress in Forensic Toxicology. *Fayixuezazhi*, *36*(2).

Faiq, M., Kumar, A., Singh, H., Pareek, V., Qadri, R., Raza, K., Kumari, C., Narayan, R., Kumar, P., Kulandhasamy, M. and Pandey, S., 2020. COVID-19: A review on molecular basis, pathogenic mechanisms, therapeutic aspects and future projections.

Fantini, J., Di Scala, C., Chahinian, H. and Yahi, N., 2020. Structural and molecular modeling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. *International journal of antimicrobial agents*, p.105960.

FDA. 2020. Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease Available at:

https://www.fda.gov/media/136534/download. Accessed April 1, 2020.

Gallagher, T.M. and Buchmeier, M.J., 2001. Coronavirus spike proteins in viral entry and pathogenesis. *Virology*, *279*(2), pp.371-374.

Gao, J. and Hu, S., 2020. Update on use of chloroquine/hydroxychloroquine to treat coronavirus disease 2019 (COVID-19). *BioScience Trends*.

Gao, J., Tian, Z. and Yang, X., 2020. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience trends*.

García-Serradilla, M., Risco, C. and Pacheco, B., 2019. Drug repurposing for new, efficient, broad spectrum antivirals. *Virus research*.

Gordon, C.J., Tchesnokov, E.P., Woolner, E., Perry, J.K., Feng, J.Y., Porter, D.P. and Gotte, M., 2020. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *Journal of Biological Chemistry*, pp.jbc-RA120.

Holshue, M.L., DeBolt, C. and Lindquist, S., 2020. First Case of 2019 Novel Coronavirus in the United All rights reserved. No reuse allowed without permission. the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. States.*NEngl J Med*, *10*.

Huang, M., Tang, T., Pang, P., Li, M., Ma, R., Lu, J., Shu, J., You, Y., Chen, B., Liang, J. and Hong, Z., 2020. Treating COVID-19 with Chloroquine. *Journal of molecular cell biology*.

Ko, W.C., Rolain, J.M., Lee, N.Y., Chen, P.L., Huang, C.T., Lee, P.I. and Hsueh, P.R., 2020. Arguments in favour of remdesivir for treating SARS-CoV-2 infections. *International Journal of Antimicrobial Agents*.

Li, F., Li, W., Farzan, M. and Harrison, S.C., 2005.Structure of SARS coronavirus spike receptor-binding domain complexed with receptor.*Science*, *309*(5742), pp.1864-1868.

Li, W., Moore, M.J., Vasilieva, N., Sui, J., Wong, S.K., Berne, M.A., Somasundaran, M., Sullivan, J.L., Luzuriaga, K., Greenough, T.C. and Choe, H., 2003. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*, *426*(6965), pp.450-454.

Lillie, P.J., Samson, A., Li, A., Adams, K., Capstick, R., Barlow, G.D., Easom, N., Hamilton, E., Moss, P.J., Evans, A. and Ivan, M., 2020. Novel coronavirus disease (Covid-19): the first two patients in the UK with person to person transmission. *Journal of Infection*.

Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W. and Wang, M., 2020. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell discovery*, *6*(1), pp.1-4.

Liu, W., Morse, J.S., Lalonde, T. and Xu, S., 2020. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019- nCoV. *Chembiochem*.

Lo, M.K., Feldmann, F., Gary, J.M., Jordan, R., Bannister, R., Cronin, J., Patel, N.R., Klena, J.D., Nichol, S.T., Cihlar, T. and Zaki, S.R., 2019. Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. *Science translational medicine*, *11*(494), p.eaau9242.

Lo, M.K., Jordan, R., Arvey, A., Sudhamsu, J., Shrivastava-Ranjan, P., Hotard, A.L., Flint, M., McMullan, L.K., Siegel, D., Clarke, M.O. and Mackman, R.L., 2017. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and

Paramyxoviruses. *Scientific reports*, *7*, p.43395.

Marty, A.M. and Jones, M.K., 2020. The novel Coronavirus (SARS-CoV-2) is a one health issue. *One Health (Amsterdam, Netherlands)*, *9*, pp.100123-100123..

Matrosovich, M., Herrler, G. and Klenk, H.D., 2013. Sialic acid receptors of viruses. In *SialoGlyco Chemistry and Biology II* (pp. 1-28). Springer, Cham.

Menachery, V.D., YountJr, B.L., Debbink, K., Agnihothram, S., Gralinski, L.E., Plante, J.A., Graham, R.L., Scobey, T., Ge, X.Y., Donaldson, E.F. and Randell, S.H., 2015. A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nature medicine*, *21*(12), p.1508.

Millet, J.K. and Whittaker, G.R., 2015. Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. *Virus research*, *202*, pp.120-134.

Patrì, A. and Fabbrocini, G., 2020. Hydroxychloroquine and ivermectin: a synergistic combination for COVID-19 chemoprophylaxis and/or treatment?. *Journal of the American Academy of Dermatology*.

Pedersen, N.C., Perron, M., Bannasch, M., Montgomery, E., Murakami, E., Liepnieks, M. and Liu, H., 2019. Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritonitis. *Journal of feline medicine and surgery*, *21*(4), pp.271-281.

Rabaan, A.A., Al-Ahmed, S.H., Sah, R., Tiwari, R., Yatoo, M.I., Patel, S.K., Pathak, M., Malik, Y.S., Dhama, K., Singh, K.P. and Bonilla-Aldana, D.K., 2020. SARS-CoV-2/COVID-19 and Advances in Developing Potential Therapeutics and Vaccines to Counter this Emerging Pandemic Virus–A Review.

Randolph, V.B., Winkler, G. and Stollar, V., 1990. Acidotropic amines inhibit proteolytic processing of flavivirusprM protein. *Virology*, *174*(2), pp.450-458.

Rosa, S.G.V. and Santos, W.C., 2020. Clinical trials on drug repositioning for COVID-19 treatment. *Revista Panamericana de SaludPública*, *44*.

Savarino, A., Di Trani, L., Donatelli, I., Cauda, R. and Cassone, A., 2006. New insights into the antiviral effects of chloroquine.*The Lancet infectious diseases*, *6*(2), pp.67-69.

Shereen, M.A., Khan, S., Kazmi, A., Bashir, N. and Siddique, R., 2020. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *Journal of Advanced Research*.

Sheahan, T.P., Sims, A.C., Graham, R.L., Menachery, V.D., Gralinski, L.E., Case, J.B., Leist, S.R., Pyrc, K., Feng, J.Y., Trantcheva, I. and Bannister, R., 2017. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Science translational medicine*, *9*(396).

Simmons, G., Gosalia, D.N., Rennekamp, A.J., Reeves, J.D., Diamond, S.L. and Bates, P., 2005. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. *Proceedings of the National Academy of Sciences*, *102*(33), pp.11876-11881.

Simmons, G., Zmora, P., Gierer, S., Heurich, A. and Pöhlmann, S., 2013. Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research. *Antiviral research*, *100*(3), pp.605-614.

Singh, R.K., Dhama, K., Chakraborty, S., Tiwari, R., Natesan, S., Khandia, R., Munjal, A., Vora, K.S., Latheef, S.K., Karthik, K. and Singh Malik, Y., 2019. Nipah virus: epidemiology, pathology, immunobiology and advances in diagnosis, vaccine designing and control

strategies–a comprehensive review. *Veterinary Quarterly*, *39*(1), pp.26-55.

Song, W., Gui, M., Wang, X. and Xiang, Y., 2018. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. *PLoS pathogens*, *14*(8), p.e1007236.

Seitz, M., Valbracht, J., Quach, J. and Lotz, M., 2003. Gold sodium thiomalate and chloroquine inhibit cytokine production in monocytic THP-1 cells through distinct transcriptional and posttranslational mechanisms. *Journal of clinical immunology*, *23*(6), pp.477-484.

Thomé, R., Lopes, S.C.P., Costa, F.T.M. and Verinaud, L., 2013. Chloroquine: modes of action of an undervalued drug. *Immunology letters*, *153*(1-2), pp.50-57.

Tyrell, D.A., 1968. Coronaviruses. *Nature (Lond.)*, *220*, p.650.

Vincent, M.J., Bergeron, E., Benjannet, S., Erickson, B.R., Rollin, P.E., Ksiazek, T.G., Seidah, N.G. and Nichol, S.T., 2005.Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virology journal*, *2*(1), p.69.

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W. and Xiao, G., 2020.Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell research*, *30*(3), pp.269-271.

Warren, T.K., Jordan, R., Lo, M.K., Ray, A.S., Mackman, R.L., Soloveva, V., Siegel, D., Perron, M., Bannister, R., Hui, H.C. and Larson, N., 2016.Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys.*Nature*, *531*(7594), pp.381-385.

WHO(2020).https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200418-sitrep-89-covid-19.pdf?sfvrsn=3643dd38_2

Yavuz S., Ünal, S.,2020. Antiviral treatment of COVID-19. *Turk J Med Sci*.doi: 10.3906/sag-2004-145.

Yan, Y., Zou, Z., Sun, Y., Li, X., Xu, K.F., Wei, Y., Jin, N. and Jiang, C., 2013. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. *Cell research*, *23*(2), pp.300-302.

Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P., Liu, X., Zhao, L., Dong, E., Song, C. and Zhan, S., 2020. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases*.

Zhou, D., Dai, S.M. and Tong, Q., 2020. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *Journal of Antimicrobial Chemotherapy*.

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