REVIEW PAPER

COVID-19 possible medical treatments

Marzieh Mohammadi [1,2*], Zahra Khoddamipour [3], Nafiseh Bagheri [3]

[1] Department of Pharmaceutics, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

[2] Targeted Drug Delivery Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[3] Department of Medical Biotechnology and Nanotechnology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

ARTICLE INFO

Article History:
Received 29 October 2020
Accepted 22 December 2020
Published 01 January 2021

Keywords:
SARS-CoV-2
COVID-19
medicine, Remdesivir
Lopinavir/ritonavir
Hydroxychloroquine
Favipiravir

ABSTRACT

Recent outbreak of SARS-CoV-2 virus and its high incidence has made national and international health authorities focus on evaluation and development of medicines to fight against severe cases of the Coronavirus-19 disease (COVID-19). COVID-19 is a pneumonia like infectious disease which was first reported in in Wuhan, Hubei, China in December 2019. Due to the fast evolving pandemic, there are many clinical trials assessing the efficiency of anti-inflammatory agents (e.g. chloroquine and Hydroxychloroquine, azithromycin and NSAIDS) antiviral agents (e.g. oseltamivir, Remdesivir, Favipiravir, Lopinavir/ritonavir, ribavirin, Umifenovir) and immunomodulatory medicines such as interferons. Herein, we are going to introduce currently used medicines, their mechanisms of action and the associated adverse effects. Thereafter, possible nanopharmaceuticals with disinfectant or medicinal properties are discussed. Given the current available literature, among different medicines, Remdesivir which is an antiviral agent with RNA polymerase inhibitor mechanism of action showed acceptable results and there are controversies in the efficacy of other medications.

How to cite this article
Mohammadi M., Khoddamipour Z., Bagheri N. COVID-19 possible medical treatments. Nanomed Res J, 2021; 6(1): 1-10.
DOI: 10.22034/nmrj.2021.01.001

INTRODUCTION

Coronovirus disease 2019 (COVID-19) is a pneumonia like infectious disease which was first reported in in Wuhan, Hubei, China in December, 2019. The name of the virus causing COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was selected by the International Committee on Taxonomy of Viruses [1]. The clinical indications considerably resembles viral pneumonia. However, sequence analysis studies revealed the emersion of a novel coronavirus [2]. To date (July 2, 2020) there are 10.7 million confirmed cases of COVID-19 with 5.46 million recovered and 516000 cases of death all around the world [3]. In Iran, there are 230,000 confirmed cases of COVID-19 patients with 191,000 recovered cases and 11,000 death [4].

* Corresponding Author Email: *mohammadimz@mums.ac.ir*

Coronaviruses (CoVs) are classified in the subfamily of Orthocoronavirinae belonging to the family Coronaviridae and the Order Nidovirales. It was found that there are four species within the subfamily of Orthocoronavirinae which are named Alpha- coronavirus, Beta-coronavirus, Delta-coronavirus and Gamma-coronavirus [5].

Coronaviruses are made of enveloped, single, positive-stranded RNA genome encoding four membrane proteins named spike, envelope, membrane and nucleocapsid proteins [6] which are pivotal for its assembly and infection. The membrane protein is demonstrated to be the central organizer for the coronavirus assembly [7]. Rather than 4 structural proteins, SARS-CoV-2 possesses 5 accessory proteins (ORF3a, ORF6, ORF7, ORF8 and ORF9)[2]. Studies demonstrated that the principle protein responsible for entrance

of the virus to the host cells is the spike protein [6]. It provides the integration of the virus to the cell surface receptors. The envelop protein composed of 76-109 amino acid residues is an essential protein affecting the membrane permeability of the host cells and virus assembly [7]. Hemagglutinin-esterase dimer which is placed on the surface of the virus might facilitate the virus cell entrance and infecting the host cell while it is not required for its replication [8].

It was indicated that SARS-CoV-2 binds to the angiotensin converting enzyme-2 (ACE2) receptors in highly expressed organs specially the lungs [6]. ACE2 is a type I membrane protein which is expressed in lung, arteries, heart, kidney and intestine and it is generally correlated with cardiovascular diseases[9]. ACE2 is a part of renin angiotensin system which regulates the blood pressure. The principle activity of ACE2 is the hydrolysis of angiotensin 2 to angiotensin [9]. ACE2 is made of an N-terminal peptidase M2 domain and a C terminal Collectrin-like domain [10]. The sequence analysis of S protein of SARS-CoV-2 revealed that it conjugates to human ACE2 10–20 folds more than SARS-CoV [11]. That might be the reason of its high potential to infect humans.

Studies indicated that the incubation period of COVID-19 is about 5.2 days. The main symptoms at the onset of the disease are cough, fever, fatigue and the shortness of breath. Other revealed symptoms are haemoptysis, diarrhea, dyspnea, grand-glass opacities, headache and lymphopenia [12].

It was demonstrated that in most cases, it took about 6-41 days (median of 14) from the onset of the disease to the death state [13]. The duration is considerably dependent on the age of the patients and their immune system. Rather than pneumonia like symptoms, it could lead to systemic disorders such as acute cardiac injury and hypoxia [14]. Additionally, a recent study indicated that the enteric symptoms of COVID-19 are due to involvement of enterocytes expressing ACE2 proving that SARS-CoV-2 invades other organs than respiratory tract [15].

SARS-CoV-2 is transmitted through respiratory droplets. Also there is a possibility of transmission through aerosol in closed environment. However, the transmission of the virus from the mother to the new born and its secretion to the breast milk has not been reported yet 2.

Until now there is not any certainly confirmed medicine against SARS-CoV-2 and current treatments are predominantly based on management of the symptoms. The main administered treatments are categorized into antivirals, immunomodulators (ie. interferons) and anti-inflammatory agents.

In the current study, we are going to discuss possible mechanism of action of each medicine, the adverse reactions and their efficiency. Afterwards, we will introduce nanotechnology based disinfectants and treatments against SARS-CoV-2.

DIFFERENT MEDICATIONS

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxy Chloroquine are antimalaria agents which have been used since 1940 [16]. Hydroxy Chloroquine is an analogue of Chloroquine and show similar pharmacokinetics. Both drugs were also used in autoimmune diseases such as rheumatoid arthritis or lupus as anti-inflammatory agents [17]. The possible mechanisms of these drugs against SARS-CoV-2 and other viruses are listed in Table 1. Studies demonstrated that SARS-CoV-1 enters the cells though binding to DC-SIGN receptor. The low pH of endosomes provides fusion of the membranes of the virus and the target cell leading to the release of the viral genome into the cytosol [18]. The inhibitory mechanism of chloroquine is rapid elevation of endosomal pH leading to interruption of endosomal fusion [19]. The possible action of chloroquine on the replication cycle of the virus could be inhibiting the virion budding in Golgi complex through inactivation of M protein [20] because the same mechanism was proved for Dengue-2 virus in which chloroquine interferes with proteolytic conversion of the flavivirus prM protein to M protein inhibiting its viral replication [21]. Chloroquine is also an effective immunomodulatory agent which was proved to inhibit expression of IL-1 ß [22], reduced IL-1 and IL-6 [23] and inhibited the production of TNFα through interfering with cellular iron metabolism [24], inhibiting alteration of pro-TNF into mature TNFα molecules [25] and/or blockade of mRNA expression of TNFα [22, 26].

Due to the fact that the use of CQ and HCQ might prolong the QT interval (QTc), before starting administration, electrocardiography is essential. Besides, coadministration of drugs with prolonging the QTc is prohibited. However, in clinical protocols concurrent use of macrolides such as azithromycin and antiviral agents such as lopinavir/ritonavir

Table 1. Possible mechanisms of action of chloroquine and hydroxychloroquine against different viruses and inflammatory diseases [28].

Name of the virus	Possible mechanism of action	References
-Human coronavirus HCoV-O43 -Orthomyxoviruses	interfering with viral entrance through inhibition of synthesis of sialic acid and ligand recognition by the virus.	[29-31]
-Enveloped viruses such as Dengue virus or Chikungunya virus	inhibiting virus replication through interfering with pH-dependent endosome mediated viral entrance	[32, 33]
-HIV virus	inhibiting the post-translational modification of viral proteins such as in inhibiting glycosylation of the gp120 envelope glycoprotein of HIV virus	[34, 35]
- Dengue-2 virus	interfering with proteolytic processing of the flavivirus prM protein to M protein so that inhibiting the replication of the virus	[21]
	impair proper maturation of viral proteins through pH modulation	[21]
	rising the transport of soluble antigens	[36]
	into the cytosol of dendritic cells and the improving the human cytotoxic CD8+ Tcell responses	
	Regulation of proinflammatory cytokines through reduction of interleukin-1 beta (IL-1ß), IL-6 and TNFα.	[22-25]
-HCoV-229 coronavirus	blocking	[37, 38]
	phosphorylation of the p38 mitogen-activated protein kinase in	
	THP-1 cells as well as caspase-1 so that inhibiting virus replication cycle	

with HCQ/CQ are performed. In such cases, close observation of QTc is essential. Another important issue is that G6PD deficiency, retinopathy, pre-existing maculopathy and epilepsy are the contraindications of using CQ and HCQ [27].

Azithromycin

Previous studies demonstrated that macrolides such as erythromycin and azithromycin possess simultaneous anti-bacterial and anti-inflammatory effects [39]. Macrolides reduce the synthesis of IL-8 and IL-6 and also inhibit nuclear factor (NF)-kB so that suppress neutrophil attraction to the site of the infection [40, 41]. Additionally, preliminary studies showed that they might also have antiviral properties [42]The anti-bacterial properties is through the inhibition of bacterial protein synthesis. Some studies demonstrated that due to the anti-inflammatory and antiviral properties of macrolides, combination therapy of COVID-19 patients with azythromycin and hydroxychloroquine synergistically reduces the viral load [43, 44].

An open-label non-randomized clinical trial evaluated the synergistic effect of azithromycin and chloroquine on respiratory viral load of COVID-19 patients. The results showed that the use of azithromycin reinforced the viral clearance of chloroquine [43, 45]. However, retrospective multicenter cohort study of 25 hospitals in New York metropolitan region indicated that there is no significant difference in in-hospital mortality among patient received Hydroxychloroquine, azithromycin, both or neither of them [46]. Moreover, the studies proved that the risk of QT Interval prolongation is increased in patients who received both drugs [47]. That is the reason clinicians closely observe cardiac adverse events esp. QT interval. Another study on 201 patients with COVID-19 at 3 hospitals within the Northwell Health system showed that torsade de pointes

Was not observed in any of the patients and there was not any difference in baseline corrected QT interval of patients received mono or combination therapy although maximum corrected QT interval was remarkably more in the patients with combination therapy versus the monotherapy group [48].

NSAIDs (Naproxen, diclofenac, ibuprofen) and Acetaminophen (Apotel)

To alleviate one of the main symptoms of COVID 19 (which is fever) clinicians used acetaminophen and Non-steroidal anti-inflammatory drugs (NSAIDS). NSAIDS inhibit synthesis of prostaglandin synthases 1 and 2 which are also named as COX1 and COX2. These enzymes are responsible for synthesis of prostaglandins and lipids which trigger fever and pain. Diclofenac and celecoxib both selectively inhibit COX2 which leads to suppression of inflammation and fever. However, other non-selective NSAIDS such as ibuprofen suppress both COXs.

Another important issue is that it is not clear whether NSAIDS cause severe COVID 19 symptoms as PGD2, PGI2 and PGE2 are able

to promote or prevent inflammation [49]. On 16th March 2020, The Belgian Federal Agency for Medicines and Health Products stated that 'It is well known that NSAIDs and corticosteroids can lead to serious complications'. Besides, French authorities also recommended that use of ibuprofen is harmful for patients with COVID 19 [50]. which could be due to the assumption that use of ibuprofen might lead to over expression of ACE 2 (Angiotensin converting enzyme) receptors. ACE is expressed by epithelial enzymes of lungs, intestine, kidney and blood vessels and it is indicated that SARS-CoV and SARS-CoV-2 viruses enter the target cells through ACE receptor [51]. ACE receptor is also overexpressed in diabetic patients and those using antihypertensives such as ACE inhibitors or type 2 ARBs (angiotensin receptor blocker).

However, European Medicines Agency (EMA) reported that there is no clear evidence to confirm the relationship between NSAIDS and severe COVID 19 and it is suggested to use such medicine in the minimum effective dose and the shortest possible period [52].

Until now there is not any clinical study which proves the higher mortality rates in patients using NSAIDs or ibuprofen but generally it is recommended to use acetaminophen instead of ibuprofen in patients without the a physician's prescription [53].

Antivirals (oseltamivir, Remdesivir, Favipiravir, Lopinavir/ritonavir, ribavirin, Umifenovir)

Oseltamivir is an antiviral agent (neuraminidase inhibitor) which was approved for treatment of influenza A and B to inhibit the spreading of the virus throughout the body [54]. The clinical study performed by Wang et al. in wuhan indicated that oseltamivir did not show any significant outcomes [55]. However, there are several ongoing clinical trials evaluating combinational therapy using oseltamivir with chloroquine and favipiravir [56].

Remdesivir (GS-5734, adenosine analog) which is a broad spectrum antiviral agent showed efficient activity in the treatment of lethal Ebola [57]. It is a RNA polymerase inhibitor which disrupts the replication of the virus. Sheahan et al. demonstrated that administration of the drug immediately after the onset of the disease leads to the decrease of the virus load and improvement of pulmonary function in Ces1c (−/−) mouse SARS model [58]. However, they claimed that in case of advanced pulmonary lesions even reduction of the virus titer could not improve the survival rate. In a case report by New England Journal of Medicine, remdesivir was administrated to a patient with COVID-19 intravenously, on the 7th day of the admission. The clinical symptoms of the patient on the 8th day and the oxygen saturation increased to 94% [59]. A randomized, double-blind, placebo-controlled, multicenter trial was done at ten hospitals in Hubei, China. They demonstrated that administration of remdesivir led to a non-significant numerically faster time to clinical improvement than those receiving placebo. They also implied that in patients with severe COVID-19, remdesivir did not show significant clinical benefits while its beneficial effects in reducing the time to clinical improvement in other patients should be studied in larger populations [60]. However, Beigel et al. demonstrated that remdesivir was more efficient in comparison to placebo in reducing the time to recovery and decreasing the rate of lower respiratory tract infection [61].

Favipiravir is a purine nucleoside analog and a broad-spectrum antiviral agent which was approved in Japan for the treatment of influenza [62]. Besides, a proof-of-concept trial with favipiravir was carried out in Guinea during the outbreak of Ebola which indicated an enhanced survival trend [63]. Besides, a retrospective study of patients with Ebola disease revealed that the administration of favipiravir enhanced the survival rate and reduced the virus titer by >100 folds compared to those who received WHO-recommended treatment [64].

In a study by Cai et al., patients with positive COVID-19 test were divided in to two groups: The first one received favipiravir orally (Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice daily) and IFN-α (5 million U) twice daily by inhalation. Lopinavir (LPV)/ritonavir (RTV) (Days 1–14: 400 mg/100 mg twice daily) and inhalation IFN-α (5 million U twice daily) was administered to the other group as a control. The results revealed enhanced improvement in the chest imaging in comparison with the control. Besides, favipiravir led to better therapeutic responses in terms of virus titer and disease progression [65].

Ritonavir is a HIV-1 protease inhibitor which was approved in 1996 for use in patients with HIV-1. Lopinavir is an active form of RTV with invitro EC_{50} of 10 folds lower than RTV. From the invitro studies, RTV/LPV was first suggested as an effective agent to inhibit the protease activity of coronavirus [66]. However, further studies revealed that it

Table 2. Several antiviral drugs used against SARS-CoV-2.

	Mechanism of action	Details	References
Oseltamivir	neuraminidase inhibitor	-was approved for treatment of influenza in adults in 1999. - did not show promising results in patients with COVID-19	[68] [55]
Remdesivir	RNA polymerase inhibitor	For the treatment of COVID-19, it was permitted for emergency use in the US, India, Singapore, and approved in Japan for use in patients with severe disease. Also it was approved in UK in May 2020.	[69] [70] [71] [72]
Favipiravir	Protease inhibitor	-Approved to treat influenza in Japan in 2014 - Showed promising results against Ebola - Approved for use in clinical trials of COVID 19 in China.	[73] [63] [74]
Lopinavir	Protease inhibitor	-Approved in 2000 for use in patients with HIV-1 - The combination with Lopinavir did not show significant effectiveness against Sars-Cov2	[67]
Ritonavir	Protease inhibitor	-Approved in 1996 for use in patients with HIV-1 - The combination with Lopinavir did not show significant effectiveness against Sars-Cov2	[67]
Ribavirin	interferes with RNA metabolism	- Approved for medical use in 1986 - was approved as a part of combinational therapy for treatment of patients with chronic hepatitis C	[75] [76]
Umifenovir		- was used to treat influenza in Russia and China. - A retrospective study demonstratd that Umifenovir could not enhance the prognosis or speed up SARS-CoV-2 clearance in non-ICU patients	[77]

doesn't affect the severe cases. Cao et al. conducted a randomized, controlled, open-label trial involving patients with laboratory-confirmed SARS-CoV-2 infection who received LPV/RTV and compared to the control group receiving the standard treatment. The results showed no difference in clinical improvement and viral load. Moreover, the study group showed more gastrointestinal adverse reactions whereas severe side effects were more common in the control group [67].

Interferons

Type 1 interferons (IFN-1) are a group of cytokines (made of α and β subtypes) [78]. and secreted by various cells up on identifying viral components [79]. IFN-1 are the cytokines released early in a viral infection. After binding to their receptors (IFNAR), a signaling pathway is induced leading to immunomodulation and inflammation. This process limits viral replication through decreasing the cell metabolism, inhibiting the release of cytokines, reducing membrane fluidity or inhibiting virus membrane fusion [80]. Dysregulated IFN responses is a potent immunomodulatory strategy of betacronaviruses which provides stealth replication of the virus leading to high virus titers [81]. It was demonstrated that blocking the IFN induction causes accumulation of macrophages in the lungs that leads to immunopathology in SARS-CoV or MERS-CoV infections [82]. Moreover, dysregulation of interferons in severe COVID 19 causes imbalance in pro repair and proinflammatory functions of macrophages [83]. Besides, IFNs promote survival of T cells so that in severe cases of COVID 19 impaired Tcell function manifest as lymphopenia and exhaustion of $CD4^+$ and $CD8^+$ T cells [84]. Additionally, delayed IFN response could inhibit T cell proliferation and cell death [85]. Dysregulation of IFNs in COVID 19 pathogenesis focuses the attentions to the potential of interferons for therapeutic interventions. A study evaluated the prophylactic efficiency of nasal drops of IFNα along with personal protective equipment in health care providers and the result was promising during 28 days of intervention (NCT04320238). However, the results of other clinical trials using IFNs with other drugs are inconclusive. An open-label, randomized, phase 2 trial evaluated the efficiency of a 14-day combination of lopinavir, ribavirin and three doses of interferon beta-1b on alternate days to 14 days of lopinavir and ritonavir. The results indicated the safety and superiority of the intervention. It reduced the duration of viral shedding and hospitalization combined with alleviating the symptoms [86]. A study by Sheahan et al. revealed that administration of IFNβ combined with lopinavir/ritonavir against MERS-CoV enhanced pulmonary function but could not Remarkably inhibit virus replication or the severity of the disease [58]. Besides, another study showed that in patients with severe MERS-CoV infection administration of IFNα2a in combination with ribavirin delayed mortality, however, did not

reduced the mortality rate in the long term [87].

There are many factors affecting the results of different clinical studies. The time of administration (before the viral peak load or late administration), the comorbidities or the combinational treatments can alter the results.

Possible nanopharmaceuticals

Amongst different strategies, the use of nanoparticles against SARS-CoV-2 has gained dramatic interest. Nanopharmaceuticals can be used to develop sensors to screen large populations, or due to their good viral capturing capacity, they can be used as disinfectants to reduce the viral load on surfaces and environments. Additionally, nanoparticles are used for efficient delivery of medicines and genes to the target cell making them good candidates for vaccines and drug delivery applications. In this part, we focus on antimicrobial effects of nanopharmaceuticals and their potential drug delivery capabilities.

Nanoparticles with antimicrobial effects

Until now many nanomedicines have been used as disinfectants through optimization of their physicochemical properties. Such nanomaterials could be employed in medical devices, food and surfaces as the water disinfectants. Among different inorganic materials, graphene, silver ions, silver/gold nanoparticles and possess efficient antimicrobial effects[88, 89]. The higher surface to volume ratio resulted in improved surface exposure to the microbes and more antimicrobial activity [88]. One of the major applications of silver nanoparticles could be reducing the load of airborn pathogens (ie. bacteria, fungi and viruses) in hospitals to inhibit hospital acquired infections esp. in intensive care units. Such pathogens are deposited on air-conditioning systems and multiply due to the presence of moisture [89]. Joe et al. developed silver-nanoparticle (AgNP) decorated silica particles and coated the air conditioner filter with the particles. The results proved antiviral ability of the particles in the presence of aerosolized viruses. Also, they showed that the filtration quality of air was not affected [90]. Moreover, studies demonstrated that AgNPs showed broad antiviral capabilities for Hepatitis B virus (HBV), herpes simplex viruses (HSV) and human immunodeficiency viruses (HIV) which could be attributed to the interactions with nucleic acids or the viral proteins [91]. Gold nanoparticles (AuNP) were also used to evaluate its antiviral ability. Papp et al. developed sialic acid coated AuNPs and evaluated its efficiency against influenza virus infection [92]. They indicated that AuNPs (14nm in size) were interacted with hemagglutinin placed on the surface of the virus and inhibited its cell entrance. Besides, the designed nanoparticles were nontoxic to the host cells. Copper nanoparticles (CuNPs) also possess great activity against various organisms. Fujimori et al. produced Copper(I) Iodide nanoparticles and confirmed the inactivation of H1N1 Influenza Virus after incubation with CuI nanoparticles. They demonstrated that the nanoparticles were reacted with hemagglutinin and neuraminidase causing inactivation of the virus due to formation of reactive oxygen species(ROS) [93, 94].

Nanoparticles as drug delivery agents

Due to the fact that nasal epithelium is the main place for the entrance of the virus, a local intranasal administration of antiviral nanoparticles could play an important role in blocking the virus. Besides, studies demonstrated that combination delivery of antiviral agents significantly enhanced the cell protection [97]. Nanoparticles could be used as multiple delivery agents [98]. Besides, the nanoparticles' surface could be decorated so that antiviral agents are directed to the specific cells. To this aim, Chen et al. prepared cell membrane coated magnetic nanoparticles to targeted the influenza virus. The results indicated that due to the selective binding affinity between the virus and the cells, the demonstrated approach significantly improved the treatment and diagnosis of the virus [96].

Moreover, nanoparticles are used as platforms for pulmonary drug delivery. According to the fact that lungs are the place were SARS-CoV-2 causes inflammation and tissue damage, effective localized drug delivery could be a lifesaver. With this in mind, Bioavanta-Bosti (a leader in chitosan nanoparticles research) reported the production of Novochizol™ for localized and sustained drug delivery. It is made of chitosan nanoparticles as pulmonary drug delivery agents. Chitosan nanoparticles are completely biocompatible materials which adhere to the mucus layer and lung epithelial tissue increasing the retention of the encapsulated drug and providing its sustained release.

Besides, studies showed that the combination of specific nanoparticles with antivirals enhanced the efficiency of the drug. Li et al. produced selenium nanoparticles which were functionalized with

oseltamivir. The results indicated that the designed platform showed superior antiviral effects and restricted the drug resistance. They demonstrated the oseltamivir decorated selenium nanoparticles inhibited H1N1 infection through interfering with hemagglutinin and neuraminidase activity. Also it blocked chromatin condensation and DNA fragmentation [97].

CONCLUSION

To date, no certain medicine is developed to specifically fight against COVID 19 disease. Most medications are based on alleviating the symptoms and there are inconsistent studies about the efficiency of different antivirals, anti-inflammatory and immunomodulatory agents. However, remdesivir seems to be more promising in comparison with oseltamivir or lopinavir/ritonavir as the antivirals. Alongside with clinical treatments, nanopharmaceuticals have gained dramatical interest due to the availability of targeted gene/drug delivery to the infected organs and good viral capturing capacity or to develop sensors to screen large populations. Hence, there are many unknown facts about SARS-CoV-2 virus and many clinical trials are moving towards evaluating the effectiveness of various treatment protocols and medications.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. Severe acute respiratory syndrome-related coronavirus: The species and its viruses – a statement of the Coronavirus Study Group. Cold Spring Harbor Laboratory; 2020.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu XJTl. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. 2020;395 (10223):497-506.
3. Confirmed cases of COVID-19, recoverd cases and deaths worldwide. Available at: https://news.google.com/covid19/map?hl=en-US&mid=/m/02j71&gl=US&ceid=US:en. Accessed July,2nd, 2020.
4. Available at: https://www.worldometers.info/coronavirus/country/iran/. Accessed July 2nd, 2020.
5. Li H, Liu S-M, Yu X-H, Tang S-L, Tang C-K. Coronavirus disease 2019 (COVID-19): current status and future perspectives. International Journal of Antimicrobial Agents. 2020;55(5):105951.
6. Magrone T, Magrone M, Jirillo E. Focus on Receptors for Coronaviruses with Special Reference to Angiotensin- Converting Enzyme 2 as a Potential Drug Target - A Perspective. Endocrine, Metabolic & Immune Disorders - Drug Targets. 2020;20(6):807-11.
7. Boopathi S, Poma AB, Kolandaivel P. Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. Journal of Biomolecular Structure and Dynamics. 2020:1-10.
8. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(3):241-6.
9. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses. 2020;12(4):372.
10. Turner AJ. ACE2 Cell Biology, Regulation, and Physiological Functions. The Protective Arm of the Renin Angiotensin System (RAS): Elsevier; 2015. p. 185-9.
11. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
12. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity. 2020;109:102433.
13. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. Journal of Medical Virology. 2020;92(4):441-7.
14. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity. 2020;109:102433.
15. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. Cold Spring Harbor Laboratory; 2020.
16. Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database of Systematic Reviews. 2020.
17. Sanford CA, Jong EC, Pottinger PS. The Travel and Tropical Medicine Manual E-Book: Elsevier Health Sciences; 2016.
18. Wang H, Yang P, Liu K, Guo F, Zhang Y, Zhang G, et al. SARS coronavirus entry into host cells through a novel clathrin- and caveolae-independent endocytic pathway. Cell Research. 2008;18(2):290-301.
19. Yang Z-Y, Huang Y, Ganesh L, Leung K, Kong W-P, Schwartz O, et al. pH-Dependent Entry of Severe Acute Respiratory Syndrome Coronavirus Is Mediated by the Spike Glycoprotein and Enhanced by Dendritic Cell Transfer through DC-SIGN. Journal of Virology. 2004;78(11):5642-50.
20. Klumperman J, Locker JK, Meijer A, Horzinek MC, Geuze HJ, Rottier PJ. Coronavirus M proteins accumulate in the Golgi complex beyond the site of virion budding. Journal of Virology. 1994;68(10):6523-34.
21. Randolph VB, Winkler G, Stollar V. Acidotropic amines inhibit proteolytic processing of flavivirus prM protein. Virology. 1990;174(2):450-8.
22. Seitz M, Valbracht J, Quach J, Lotz M. Gold Sodium Thiomalate and Chloroquine Inhibit Cytokine Production in Monocytic THP-1 Cells Through Distinct Transcriptional and Posttranslational Mechanisms. Journal of Clinical Immunology. 2003;23(6):477-84.
23. Jang CH, Choi JH, Byun MS, Jue DM. Chloroquine inhibits

production of TNF-α, IL-1β and IL-6 from lipopolysaccharide-stimulated human monocytes/macrophages by different modes. Rheumatology. 2006;45(6):703-10.
24. Picot S, Peyron F, Donadille A, Vuillez J, Barbe G, Ambroise-Thomas PJI. Chloroquine-induced inhibition of the production of TNF, but not of IL-6, is affected by disruption of iron metabolism. 1993;80 (1):127.
25. Jeong J-Y, Jue D-MJTJoI. Chloroquine inhibits processing of tumor necrosis factor in lipopolysaccharide-stimulated RAW 264.7 macrophages. 1997;158 (10):4901-4907.
26. Zhu X, Ertel W, Ayala A, Morrison M, Perrin M, Chaudry IJI. Chloroquine inhibits macrophage tumour necrosis factor-alpha mRNA transcription. 1993;80 (1):122.
27. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(3):241-6.
28. Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? International Journal of Antimicrobial Agents. 2020;55(5):105938.
29. Kwiek JJ, Haystead TAJ, Rudolph J. Kinetic Mechanism of Quinone Oxidoreductase 2 and Its Inhibition by the Antimalarial Quinolines†. Biochemistry. 2004;43(15):4538-47.
30. Varki A. Sialic acids as ligands in recognition phenomena. The FASEB Journal. 1997;11(4):248-55.
31. Olofsson S, Kumlin U, Dimock K, Arnberg N. Avian influenza and sialic acid receptors: more than meets the eye? The Lancet Infectious Diseases. 2005;5(3):184-8.
32. Tricou V, Minh NN, Van TP, Lee SJ, Farrar J, Wills B, et al. A Randomized Controlled Trial of Chloroquine for the Treatment of Dengue in Vietnamese Adults. PLoS Neglected Tropical Diseases. 2010;4(8):e785.
33. Gay B, Bernard E, Solignat M, Chazal N, Devaux C, Briant L. pH-dependent entry of chikungunya virus into Aedes albopictus cells. Infection, Genetics and Evolution. 2012;12(6):1275-81.
34. Savarino A, Lucia MB, Rastrelli E, Rutella S, Golotta C, Morra E, Tamburrini E, Perno CF, Boelaert JR, Sperber KJJJoAIDS. Anti-HIV effects of chloroquine: inhibition of viral particle glycosylation and synergism with protease inhibitors. 2004;35 (3):223-232.
35. Savarino A, Gennero L, Sperber K, Boelaert JR. The anti-HIV-1 activity of chloroquine. Journal of Clinical Virology. 2001;20(3):131-5.
36. Accapezzato D, Visco V, Francavilla V, Molette C, Donato T, Paroli M, et al. Chloroquine enhances human CD8+ T cell responses against soluble antigens in vivo. Journal of Experimental Medicine. 2005;202(6):817-28.
37. Briant L, Robert-Hebmann Vr, Acquaviva C, Pelchen-Matthews A, Marsh M, Devaux C. The Protein Tyrosine Kinase p56lck 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. 1998;72(7):6207-14.
38. Kono M, Tatsumi K, Imai AM, Saito K, Kuriyama T, Shirasawa H. Inhibition of human coronavirus 229E infection in human epithelial lung cells (L132) by chloroquine: Involvement of p38 MAPK and ERK. Antiviral Research. 2008;77(2):150-2.
39. Tamaoki J, Sakai N, Tagaya E, Konno K. Macrolide antibiotics protect against endotoxin-induced vascular leakage and neutrophil accumulation in rat trachea. Antimicrobial Agents and Chemotherapy. 1994;38(7):1641-3.
40. Takizawa H, Desaki M, Ohtoshi T, Kikutani T, Okazaki H, Sato M, et al. Erythromycin Suppresses Interleukin 6 Expression by Human Bronchial Epithelial Cells: A Potential Mechanism of Its Anti-inflammatory Action. Biochemical and Biophysical Research Communications. 1995;210(3):781-6.
41. Desaki M, Takizawa H, Ohtoshi T, Kasama T, Kobayashi K, Sunazuka T, et al. Erythromycin Suppresses Nuclear Factor-κB and Activator Protein-1 Activation in Human Bronchial Epithelial Cells. Biochemical and Biophysical Research Communications. 2000;267(1):124-8.
42. Jang Y, Kwon H, Lee BJERJ. Effect of clarithromycin on rhinovirus-16 infection in A549 cells. 2006;27 (1):12-19.
43. Gautret P, Lagier J-C, Parola P, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HTJIjoaa. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. 2020:105949.
44. Andreani J, Le Bideau M, Duflot I, Jardot P, Rolland C, Boxberger M, et al. In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. Microbial Pathogenesis. 2020;145:104228.
45. Suzuki T, Yamaya M, Sekizawa K, Hosoda M, Yamada N, Ishizuka S, et al. Erythromycin Inhibits Rhinovirus Infection in Cultured Human Tracheal Epithelial Cells. American Journal of Respiratory and Critical Care Medicine. 2002;165(8):1113-8.
46. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, Weinberg P, Kirkwood J, Muse A, DeHovitz JJJ. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. 2020.
47. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, et al. Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiology. 2020;5(9):1036.
48. Saleh M, Gabriels J, Chang D, Kim BS, Mansoor A, Mahmood E, Makker P, Ismail H, Goldner B, Willner JJCA, Electrophysiology. The effect of chloroquine, hydroxychloroquine and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. 2020.
49. FitzGerald GA. Misguided drug advice for COVID-19. Science. 2020;367(6485):1434.1-.
50. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? ecancermedicalscience. 2020;14.
51. Paprocki M. Nonsteroidal anti-inflammatory drugs (NSAIDs) in COVID-19 patient. Disaster and Emergency Medicine Journal. 2020.
52. Day M. Covid-19: European drugs agency to review safety of ibuprofen. BMJ. 2020:m1168.
53. Gupta R, Misra A. Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infectionwith reference to use of therapeutic and other drugs used in Co-morbid diseases (Hypertension, diabetes etc). Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(3):251-4.

54. McClellan K, Perry CM. Oseltamivir: a review of its use in influenza. Drugs, 2001;61 (2):263-283.
55. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong YJJ. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. 2020;323 (11):1061-1069.
56. Rosa S, Santos W. Clinical trials on drug repositioning for COVID-19 treatment. Revista Panamericana de Salud Pública. 2020;44:1-13.
57. Cao Y-c, Deng Q-x, Dai S-x. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Medicine and Infectious Disease. 2020;35:101647.
58. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature Communications. 2020;11(1).
59. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural AJNEJoM. First case of 2019 novel coronavirus in the United States. 2020.
60. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu QJTL. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. 2020.
61. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline SJNEJoM. Remdesivir for the treatment of Covid-19—preliminary report. 2020.
62. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proceedings of the Japan Academy, Series B. 2017;93(7):449-63.
63. Sissoko D, Laouenan C, Folkesson E, M'lebing A-B, Beavogui A-H, Baize S, Camara A-M, Maes P, Shepherd S, Danel CJPm. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea. 2016;13 (3):e1001967.
64. Bai C-Q, Mu J-S, Kargbo D, Song Y-B, Niu W-K, Nie W-M, Kanu A, Liu W-W, Wang Y-P, Dafae FJCID. Clinical and virological characteristics of Ebola virus disease patients treated with favipiravir (T-705)—Sierra Leone, 2014. 2016;63 (10):1288-1294.
65. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang YJE. Experimental treatment with favipiravir for COVID-19: an open-label control study. 2020.
66. Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus—A possible reference for coronavirus disease-19 treatment option. Journal of Medical Virology. 2020;92(6):556-63.
67. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei MJNEJoM. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. 2020.
68. FDA Medical Review Archived 2014-04-16 at the Wayback Machine, linked from Tamiflu Drug Approval Package Archived 2014-04-16. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21087_Tamiflu_medr_P1.pdf.
69. Mishra AKMaM. India approves Gilead's remdesivir to treat severe COVID-19 cases. Available at: https://www.reuters.com/article/us-health-coronavirus-india-gilead-scien/india-approves-emergency-use-of-remdesivir-to-treat-covid-19-patients-idUSKBN2390VL. Accessed Auguest 1st., 2020.
70. Geddie AAaJ. Singapore approves remdesivir drug for emergency COVID-19 treatment. Available at: https://www.reuters.com/article/us-health-coronavirus-singapore-remdesiv-idUSKBN23H17F. Accessed Auguest,1st., 2020.
71. FDA U. Coronavirus (COVID-19) update: FDA issues emergency use authorization for potential COVID-19 treatment; 2020.
72. Auwaerter P. Coronavirus COVID-19 (SARS-CoV-2). Johns Hopkins ABX Guide; 2020.
73. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacology & Therapeutics. 2020;209:107512.
74. Yangfei Z. Potential coronavirus drug approved for marketing. Available at: https://www.chinadaily.com.cn/a/202002/17/WS5e49efc2a310128217277fa3.html. Accessed Auguest 1st., 2020.
75. Fischer JG, C. Robin Analogue-based Drug Discovery.: Wiley & Sons; 2006.
76. Graci JD, Cameron CE. Mechanisms of action of ribavirin against distinct viruses. Reviews in Medical Virology. 2005;16(1):37-48.
77. Lian N, Xie H, Lin S, Huang J, Zhao J, Lin Q. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. Clinical Microbiology and Infection. 2020;26(7):917-21.
78. Samuel CE. Antiviral Actions of Interferons. Clinical Microbiology Reviews. 2001;14(4):778-809.
79. Liu Y-J. IPC: Professional Type 1 Interferon-Producing Cells and Plasmacytoid Dendritic Cell Precursors. Annual Review of Immunology. 2005;23(1):275-306.
80. Schneider WM, Chevillotte MD, Rice CM. Interferon-Stimulated Genes: A Complex Web of Host Defenses. Annual Review of Immunology. 2014;32(1):513-45.
81. Blanco-Melo D, Nilsson-Payant BE, Liu W-C, Uhl S, Hoagland D, Møller R, Jordan TX, Oishi K, Panis M, Sachs DJC. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. 2020.
82. Channappanavar R, Fehr AR, Zheng J, Wohlford-Lenane C, Abrahante JE, Mack M, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. Journal of Clinical Investigation. 2019;129(9):3625-39.
83. Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, Tang H, Nishiura K, Peng J, Tan ZJJi. Anti–spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. 2019;4 (4).
84. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cellular & Molecular Immunology. 2020;17(5):533-5.
85. Acharya D, Liu G, Gack MU. Dysregulation of type I interferon responses in COVID-19. Nature Reviews Immunology. 2020;20(7):397-8.
86. Hung IF-N, Lung K-C, Tso EY-K, Liu R, Chung TW-H, Chu M-Y, Ng Y-Y, Lo J, Chan J, Tam ARJTL. Triple

combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. 2020;395 (10238):1695-1704.
87. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. The Lancet Infectious Diseases. 2014;14(11):1090-5.
88. Einafshar E, Asl AH, Nia AH, Mohammadi M, Malekzadeh A, Ramezani M. New cyclodextrin-based nanocarriers for drug delivery and phototherapy using an irinotecan metabolite. Carbohydrate Polymers, 2018;194:103-110.
89. Alibolandi M, Mohammadi M, Taghdisi SM, Ramezani M, Abnous K. Fabrication of aptamer decorated dextran coated nano-graphene oxide for targeted drug delivery. Carbohydrate Polymers, 2017;155:218-229.
90. Deshmukh SP, Patil SM, Mullani SB, Delekar SD. Silver nanoparticles as an effective disinfectant: A review. Materials Science and Engineering: C. 2019;97:954-65.
91. Schleibinger H, Rüden H. Air filters from HVAC systems as possible source of volatile organic compounds (VOC) – laboratory and field assays. Atmospheric Environment. 1999;33(28):4571-7.
92. Joe YH, Park DH, Hwang J. Evaluation of Ag nanoparticle coated air filter against aerosolized virus: Anti-viral efficiency with dust loading. Journal of Hazardous Materials. 2016;301:547-53.
93. Thi Ngoc Dung T, Nang Nam V, Thi Nhan T, Ngoc TTB, Minh LQ, Nga BTT, et al. Silver nanoparticles as potential antiviral agents against African swine fever virus. Materials Research Express. 2020;6(12):1250g9.
94. Papp I, Sieben C, Ludwig K, Roskamp M, Böttcher C, Schlecht S, et al. Inhibition of Influenza Virus Infection by Multivalent Sialic-Acid-Functionalized Gold Nanoparticles. Small. 2010;6(24):2900-6.
95. Fujimori Y, Sato T, Hayata T, Nagao T, Nakayama M, Nakayama T, et al. Novel Antiviral Characteristics of Nanosized Copper(I) Iodide Particles Showing Inactivation Activity against 2009 Pandemic H1N1 Influenza Virus. Applied and Environmental Microbiology. 2011;78(4):951-5.
96. Antunes Filho S, dos Santos OAL, dos Santos MS, Backx BPJJoN, Nanomaterials. Exploiting Nanotechnology to Target Viruses. 2020;1 (1).
97. Chen H-W, Cheng JX, Liu M-T, King K, Peng J-Y, Zhang X-Q, et al. Inhibitory and combinatorial effect of diphyllin, a v-ATPase blocker, on influenza viruses. Antiviral Research. 2013;99(3):371-82.
98. Mohammadi M, Taghavi S, Abnous K, Taghdisi SM, Ramezani M, Alibolandi M. Hybrid Vesicular Drug Delivery Systems for Cancer Therapeutics. 2018;28 (36):1802136.
99. Chen H-W, Fang Z-S, Chen Y-T, Chen Y-I, Yao B-Y, Cheng J-Y, et al. Targeting and Enrichment of Viral Pathogen by Cell Membrane Cloaked Magnetic Nanoparticles for Enhanced Detection. ACS Applied Materials & Interfaces. 2017;9(46):39953-61.
100. Li Y, Lin Z, Guo M, Xia Y, Zhao M, Wang C, et al. Inhibitory activity of selenium nanoparticles functionalized with oseltamivir on H1N1 influenza virus. International Journal of Nanomedicine. 2017;Volume 12:5733-43.