







Review

# Antiviral Activity of Ivermectin Against SARS-CoV-2: An Old-Fashioned Dog with a New Trick— A Literature Review

Mudatsir Mudatsir <sup>1,2,3,\*</sup> , Amanda Yufika <sup>2,4</sup> , Firzan Nainu <sup>5</sup>, Andri Frediansyah <sup>6,7</sup> , Dewi Megawati <sup>8,9</sup>, Agung Pranata <sup>2,3,10</sup> , Wilda Mahdani <sup>1,2,3</sup>, Ichsan Ichsan <sup>1,2,3</sup>, Kuldeep Dhama <sup>11</sup>  and Harapan Harapan <sup>1,2,3,\*</sup> 

<sup>1</sup> Department of Microbiology, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Aceh 2311, Indonesia; wildamahdani@unsyiah.ac.id (W.M.); ichsan@unsyiah.ac.id (I.I.)

<sup>2</sup> Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Aceh 23111, Indonesia; amandayufika@gmail.com (A.Y.); agungp11@unsyiah.ac.id (A.P.)

<sup>3</sup> Tropical Disease Centre, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Aceh 23111, Indonesia

<sup>4</sup> Department of Family Medicine, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Aceh 23111, Indonesia

<sup>5</sup> Faculty of Pharmacy, Hasanuddin University, Makassar 90245, Indonesia; firzannainu@unhas.ac.id

<sup>6</sup> Research Division for Natural Product Technology (BPTBA), Indonesian Institute of Sciences (LIPI), Wonosari 55861, Indonesia; andri.frediansyah@lipi.go.id

<sup>7</sup> Department of Pharmaceutical Biology, Pharmaceutical Institute, University of Tübingen, 72076 Tübingen, Germany

<sup>8</sup> Department of Microbiology and Parasitology, Faculty of Medicine and Health Sciences, Warmadewa University, Denpasar 80239, Indonesia; amegawati@ucdavis.edu

<sup>9</sup> Department of Medical Microbiology and Immunology, School of Medicine, University of California, Davis, California, CA 95616, USA

<sup>10</sup> Department of Parasitology, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Aceh 23111, Indonesia

<sup>11</sup> Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh 243122, India; kdhama@rediffmail.com

\* Correspondence: mudatsir@unsyiah.ac.id (M.M.); harapan@unsyiah.ac.id (H.H.)

Received: 20 July 2020; Accepted: 10 August 2020; Published: 17 August 2020



**Abstract:** The coronavirus disease 2019 (COVID-19) pandemic is a major global threat. With no effective antiviral drugs, the repurposing of many currently available drugs has been considered. One such drug is ivermectin, an FDA-approved antiparasitic agent that has been shown to exhibit antiviral activity against a broad range of viruses. Recent studies have suggested that ivermectin inhibits the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), thus suggesting its potential for use against COVID-19. This review has summarized the evidence derived from docking and modeling analysis, in vitro and in vivo studies, and results from new investigational drug protocols, as well as clinical trials, if available, which will be effective in supporting the prospective use of ivermectin as an alternative treatment for COVID-19.

**Keywords:** SARS-CoV-2; COVID-19; ivermectin; treatment; antiviral

## 1. Introduction

In December 2019, the novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in central China [1,2]. As of 30 July 2020, more than 16 million confirmed cases and more than 600,000 deaths have been reported in 188 countries based on the COVID-19 Dashboard database [3]. Most SARS-CoV-2 infections are asymptomatic or

result in mild symptoms, such as cough, fatigue, and myalgia [4]; however, up to 20.3% of hospitalized patients require admission to the intensive care unit (ICU) [5]. The data suggest that dysregulation of the host immune response contributes to disease progression and severity [6].

COVID-19 is a global threat to public health and no effective vaccines or pharmaceutical agents against SARS-CoV-2 are available [1,4]. To respond to the pandemic, a long list of potential drugs has been proposed as potential treatments for COVID-19; some of these have been selected for clinical trials in many countries [7,8]. In accordance with the concept of drug repurposing, these prospective drugs, which are either already marketed as antivirals or have been chosen from different pharmacological classes, have been suggested to provide antiviral activity against SARS-CoV-2 infection and/or to improve the pathological symptoms of COVID-19 [7,8]. The drugs span from current antivirals to antiparasitic agents, such as protease inhibitors [9–12], nucleoside analogs [13,14], chloroquine, and hydroxychloroquine [14–17].

Among the drugs repurposed for COVID-19 is ivermectin, an FDA-approved antiparasitic agent with antiviral activity against a broad range of viruses, such as influenza [18], human immunodeficiency virus (HIV) [19], dengue virus [20], West Nile virus [21], and Venezuelan equine encephalitis virus [22]. An initial *in vitro* study suggested that ivermectin could inhibit SARS-CoV-2 [23]. In this review, we have summarized the evidence from docking and modeling studies, *in vitro* and *in vivo* studies, new investigational drug protocols, and, where available, clinical trials; from this evidence, we aim to evaluate the potency of ivermectin for use as a treatment option for COVID-19.

## 2. Materials and Methods

We searched for relevant articles on PubMed and Google Scholar using the search terms “coronavirus”, OR “SARS-CoV”, OR “MERS-CoV”, OR “SARS-CoV-2” AND “ivermectin” in the title or abstract. Available clinical trials assessing the efficacy of ivermectin were searched for on the ClinicalTrials.gov database. Available publications were discussed based on the study types (*in vitro*, *in vivo*, emergency use in hospitals, and clinical trials). All available articles until 10 May 2020 were considered eligible. All studies were discussed narratively. To build our discussion, previous studies assessing the antiviral effect of ivermectin against other viruses and its action mechanisms were also searched and discussed.

## 3. Ivermectin: An Introduction

Ivermectin is an antiparasitic agent with broad spectrum activity, high efficacy, and a wide safety margin. It has been in common use in veterinary medicine since 1981 for the treatment of onchocerciasis and filariasis [24]. Ivermectin was first used in humans in 1987 for the treatment of onchocerciasis; currently, it is approved in many countries for the treatment of onchocerciasis, filariasis, strongyloidiasis, and scabies [25]. Over the past three decades, approximately 3.7 billion doses of ivermectin have been distributed worldwide through mass drug administration (MDA) campaigns [26].

Ivermectin is available in multiple forms, including tablets, capsules, and an oral solution; however, it is only approved for administration via the oral route for humans. Studies of the metabolism of ivermectin in humans are limited; however, it was suggested that the drug is extensively metabolized in the liver [25]. The elimination half-life of ivermectin is approximately 24 h, although a previous study suggested that the drug persisted for several months after a single dose of ivermectin [27]. Ivermectin is distributed widely throughout the body, owing to its high lipid solubility, and binds strongly to plasma proteins, particularly serum albumin, and is notably excreted in feces [25].

A previous study suggested an antagonistic effect of ivermectin on vitamin K after hematoma swellings were reported in two out of 28 ivermectin-treated patients, along with a significantly increased prothrombin time of between 1 week and 1 month after drug administration [28]. Notably, even though the reduction of factor II and factor VII levels was reported to occur in most of the patients, bleeding complications were not observed in any patients [28].

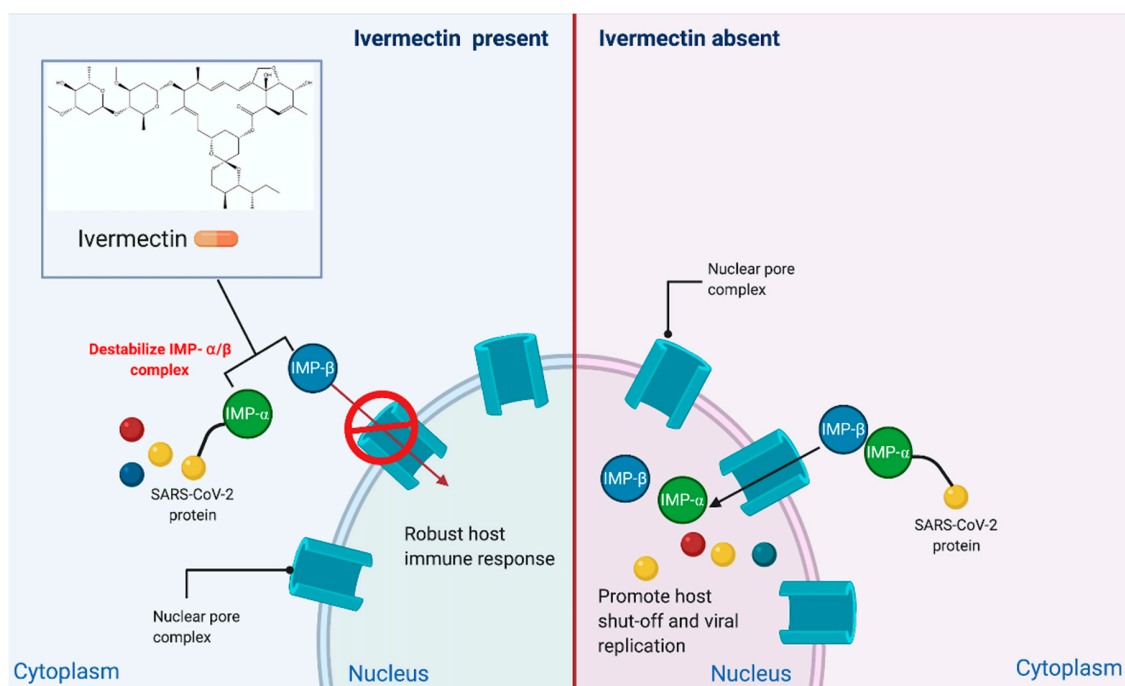
Despite being approved as an antiparasitic agent, ivermectin has also been shown to exert antiviral activity against a broad range of viruses *in vitro*. It was suggested that ivermectin inhibited the action of the integrase of HIV [19] and non-structural protein 5, a polymerase, in dengue virus [20]. In addition, ivermectin exerted inhibitory activities against several RNA viruses, such as West Nile virus [21], Venezuelan equine encephalitis virus (VEEV) [22], and influenza [18]. This antiviral effect was not only demonstrated against RNA viruses, but was also shown to be effective against a DNA virus, pseudorabies virus (PRV), both *in vitro* and *in vivo* [29].

Ivermectin binds importin (IMP) $\alpha$  armadillo (ARM) repeat domain, which causes IMP $\alpha$  thermal instability and  $\alpha$ -helicity that prevents IMP $\alpha$ -IMP $\beta$ 1 interaction [30]. Ivermectin is also able to dissociate the IMP $\alpha$ / $\beta$ 1 heterodimer, which further inhibits NS5-IMP $\alpha$  interaction within cells [30]. A significant increase in the ratio of free IMP $\alpha$  to IMP $\alpha$ / $\beta$ 1 was observed when the IMP $\alpha$ / $\beta$ 1 heterodimer was incubated with 12.5  $\mu$ M ivermectin, suggesting that ivermectin binds IMP $\alpha$  directly to impact the IMP $\alpha$  structure, most likely within the ARM repeat domain [30]. In short, ivermectin affects the IMP $\alpha$ / $\beta$ 1 recognition of viral and other proteins by preventing its formation or dissociating the heterodimer, which is crucial in the nuclear transport of viral proteins. As the replication cycle of the virus and the inhibition of the host's antiviral response occur in a manner dependent on the nuclear transport of viral proteins, targeting the transport process may be a feasible pharmacological approach for dealing with RNA viral infections [21,30,31]. In PRV, ivermectin inhibited viral entrance into the cell nucleus, as well as viral proliferation, in a dose-dependent manner [29]. The drug significantly reduced viral DNA synthesis, inhibited virus production, and blocked DNA polymerase accessory subunit UL42 entrance into the nucleus by targeting the nuclear localization signal in the transfected cells [29]. Moreover, the administration of ivermectin increased the survival rates of Ross River virus (RRV)-infected mice, most likely by relieving the infection of the infected host [29]. The broad-spectrum antiviral activity of ivermectin is believed to be due to its nuclear inhibitory activity [31,32].

#### 4. Ivermectin and SARS-CoV-2 Infection

There are no antiviral drugs available to treat SARS-CoV-2 infection. However, several clinical trials are in progress to explore the potential antiviral activities of some drugs. Although most of these drugs were initially designed for other pathogens, they appear to have the potential to treat COVID-19, either by acting directly on the virus or modulating the human immune system [30]. One of the drugs with the potential for COVID-19 treatment is ivermectin. This antiparasitic drug has shown potential antiviral activity by inhibiting the nuclear transport of viral proteins [18–22].

Previous studies on SARS-CoV proteins have shown the potential role of IMP $\alpha$ / $\beta$ 1 during infection in the signal-dependent nucleocytoplasmic shuttling of the SARS-CoV nucleocapsid protein, which may affect host cell division [21,33]. Moreover, open reading frame (ORF) 6, as the accessory protein of SARS-CoV, has been shown to have an antagonistic effect against the antiviral activity of the STAT1 transcription factor [34]. As ivermectin has shown a potential inhibitory effect on nuclear transport, particularly by preventing IMP $\alpha$ / $\beta$ 1 binding, it may also act on SARS-CoV-2. As SARS-CoV-2 is very similar to SARS-CoV, it is suggested that ivermectin may also be effective against SARS-CoV-2 by inhibiting its nuclear transport [25]. A proposed schematic figure of the antiviral action of ivermectin against SARS-CoV 2 is depicted in Figure 1.



**Figure 1.** Ivermectin inhibits SARS-CoV-2 protein transport to the nucleus.

#### 4.1. *In Vitro and In Vivo Studies*

An *in vitro* study demonstrated that a single dose of ivermectin was able to limit SARS-CoV-2 replication within 24–48 h, very likely through the inhibition of the  $\text{IMP}\alpha\beta$ 1-mediated nuclear import of viral proteins [23]. In that study, the levels of viral RNA released from the infected cells and cell-associated viral RNA were significantly reduced by more than 90% and 99%, respectively, at 24 h post infection. Furthermore, the treatment of SARS-CoV-2-infected cells with ivermectin for 48 h was shown to result in a dramatic reduction of viral RNA (by ~5000-fold) compared with the control group. However, no further reduction in viral RNA was observed at 72 h [23]. Lastly, the study suggested that no toxicity of ivermectin was observed in either group at any time point, which agreed with previous studies [19,20,22]. There was no clear explanation of how ivermectin achieved its antiviral properties against SARS-CoV-2, but it was believed to function in same way as it did against other viruses.

SARS-CoV-2 protein is translocated into the nucleus through the nuclear pore complex (NPC) via binding to the importin- $\alpha$  (IMP- $\alpha$ ) and importin- $\beta$  (IMP- $\beta$ ) heterodimer. Once in the nucleus, the SARS-CoV-2 protein is released by the importin- $\alpha/\beta$  complex. The SARS-CoV-2 protein then promotes host shut-off, which results in the reduction of the host immune response, thereby allowing the virus to replicate. Ivermectin inhibits SARS-CoV-2 protein translocation into the nucleus by binding to the importin- $\alpha/\beta$  complex and destabilizing the importin- $\alpha/\beta$  heterodimer. The ivermectin treatment most likely promotes host immune responses to occur in an efficient manner.

There has been increased public interest in ivermectin after the study showed the effect of the drug on SARS-CoV-2 *in vitro*. The Food and Drug Administration (FDA) even responded to this study by issuing an official letter to emphasize that research was still at the very early stage and to highlight the need to conduct further phases of clinical trials to determine if ivermectin is effective in the treatment of COVID-19. This is important, as the study may lead to the high-risk practice of self-medication by consumers [35]. Regardless of the controversy, this study is an important milestone for further research on the effect of ivermectin on SARS-CoV-2 infection.

#### 4.2. Results from Patients

The drug combination of ivermectin and hydroxychloroquine was proposed as a combination therapy for the prophylaxis or treatment of COVID-19. This combination may produce a synergistic effect with the inhibition of both viral entry and viral replication [36]. However, pharmacokinetic analysis indicated that a higher dosage was required to replicate the antiviral activity. Therefore, the recommended inhibitory concentration is very difficult to reach in humans [37]. In addition, although hydroxychloroquine has been approved by the FDA as an Emergency Use Authorization (EUA) against COVID-19, its efficacy is questioned [38] and its usage against SARS-CoV-2 is still highly controversial [39,40]. Further randomized clinical controlled studies are required to come to a conclusion about the efficacy of ivermectin in patients with SARS-CoV-2.

#### 4.3. Ongoing Clinical Trials

Several clinical trials are ongoing in various countries, including India, the USA, Egypt, and Iraq, to assess the efficacy of ivermectin for COVID-19. The list of the current ongoing clinical trials is presented in Table 1. The results of these clinical trials will provide robust information on the efficacy of ivermectin for COVID-19 treatment.

**Table 1.** A list of ongoing registered clinical trials of ivermectin to treat COVID-19.

Identifier Number	Title	Expected Participants	Length of Treatment	Ivermectin Dose	Location
NCT04373824	Max ivermectin-COVID 19 study versus standard of care treatment for COVID 19 cases. A pilot study	50	2 days	200–400 µg per kg body weight + standard treatment	India
NCT04374279	Trial to promote recovery from COVID-19 with ivermectin or endocrine therapy	60	3 days (with possible extension up to 6 days)	600 µg/kg (up to a maximum dose of 60 mg)	USA
NCT04360356	Ivermectin and nitazoxanide combination therapy for COVID-19	100	6 days	200 µg/kg once orally on empty stomach plus nitazoxanide 500 mg twice daily orally with meal	Egypt
NCT04343092	Ivermectin adjuvant to hydroxychloroquine and azithromycin in COVID19 patients	50	No information	12 mg/week + hydroxychloroquine 400 mg/day + azithromycin 500 mg daily	Iraq
NCT04351347	The efficacy of ivermectin and nitazoxanide in COVID-19 treatment	60	No information	Combined with chloroquine (no information about dose)	Egypt
NCT04374019	Novel agents for treatment of high-risk COVID-19 positive patients	240	2 days for ivermectin +14 days for hydroxychloroquine	First 2 days: Weight < 75 kg: four tablets (12 mg total daily dose). Days 1–2: Weight > 75 kg: five tablets (15 mg total daily dose) in combination with hydroxychloroquine. Days 1–14: three tablets (600 mg total daily dose)	USA
NCT04345419	A real-life experience on treatment of patients with COVID 19	120	No information	As a single dose (no information)	Egypt

## 5. Conclusions

Ivermectin is an antiparasitic drug with potential use as a broad-spectrum antimicrobial agent for the treatment of viral infections. Initial evidence indicated that ivermectin, an importin  $\alpha/\beta 1$ -mediated nuclear import inhibitor, inhibited SARS-CoV-2 in vitro. In a small clinical study, the administration of ivermectin (150 µg/kg) in hospitalized patients with COVID-19 was associated with a lower mortality rate and a shorter hospital stay. Several randomized controlled trials are ongoing to investigate the efficacy of ivermectin against COVID-19. In addition to ivermectin, several drugs either currently classified as an antiviral or alternative class of drug, have been the subject of clinical trials as a part

of the drug repurposing effort in the fight against COVID-19. The results of these clinical trials are required to confirm the efficacy of these drugs for the treatment of patients with COVID-19.

**Author Contributions:** Conceptualization, H.H.; validation, M.M., A.Y., F.N., A.F., D.M., A.P., W.M., I.I., K.D., and H.H.; writing—original draft preparation, M.M., A.Y., F.N., D.M., and H.H.; writing—review and editing, M.M., A.Y., F.N., A.F., D.M., A.P., W.M., I.I., K.D., and H.H. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Malik, Y.S.; Kumar, N.; Sircar, S.; Kaushik, R.; Bhatt, S.; Dhama, K.; Gupta, P.; Goyal, K.; Singh, M.P.; Ghoshal, U.; et al. Pandemic Coronavirus Disease (COVID-19): Challenges and A Global Perspective. *Preprints* **2020**, *9*, 519. [[CrossRef](#)] [[PubMed](#)]
2. Chatterjee, P.; Nagi, N.; Agarwal, A.; Das, B.; Banerjee, S.; Sarkar, S.; Gupta, N.; Gangakhedkar, R.R. The 2019 novel coronavirus disease (COVID-19) pandemic: A review of the current evidence. *Indian J. Med. Res.* **2020**, *154*, 147. [[CrossRef](#)] [[PubMed](#)]
3. Dong, E.; Du, H.; Gardner, L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect. Dis.* **2020**, *20*, 533–534. [[CrossRef](#)]
4. Harapan, H.; Itoh, N.; Yufika, A.; Winardi, W.; Keamg, S.; Te, H.; Megawati, D.; Hayati, Z.; Wagner, A.; Mudatsir, M. Coronavirus disease 2019 (COVID-19): A literature review. *J. Infect. Public Health* **2020**, *13*, 667–673. [[CrossRef](#)] [[PubMed](#)]
5. Rodriguez-Morales, A.J.; Cardona-Ospina, J.A.; Gutierrez-Ocampo, E.; Villamizar-Pena, R.; Holguin-Rivera, Y.; Escalera-Antezana, J.P.; Alvarado-Arnez, L.E.; Bonilla-Aldana, D.K.; Franco-Paredes, C.; Henao-Martinez, A.F.; et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med. Infect. Dis.* **2020**, *34*, 101623. [[CrossRef](#)] [[PubMed](#)]
6. Keam, S.; Megawati, D.; Patel, S.; Tiwari, R.; Dhama, K.; Harapan, H. Immunopathology and immunotherapeutic strategies in SARS-CoV-2 infection. *Rev. Med. Virol.* **2020**. [[CrossRef](#)]
7. Xia, S.; Liu, M.; Wang, C.; Xu, W.; Lan, Q.; Feng, S.; Qi, F.; Bao, L.; Du, L.; Liu, S.; et al. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. *Cell Res.* **2020**, *30*, 343–355. [[CrossRef](#)]
8. Sanders, J.M.; Monogue, M.L.; Jodlowski, T.Z.; Cutrell, J.B. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* **2020**, *323*, 1824–1836. [[CrossRef](#)]
9. Wang, J. Fast Identification of Possible Drug Treatment of Coronavirus Disease -19 (COVID-19) Through Computational Drug Repurposing Study. *J. Chem. Inf. Model* **2020**, *60*, 3277–3286. [[CrossRef](#)]
10. Liu, X.; Wang, X.-J. Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines. *J. Genet. Genom.* **2020**, *47*, 119–121. [[CrossRef](#)]
11. Fintelman-Rodrigues, N.; Sacramento, C.Q.; Lima, C.R.; da Silva, F.S.; Ferreira, A.; Mattos, M.; de Freitas, C.S.; Soares, V.C.; Dias, S.D.S.G.; Temerozo, J.R. Atazanavir inhibits SARS-CoV-2 replication and pro-inflammatory cytokine production. *BioRxiv* **2020**. [[CrossRef](#)]
12. Hall, D.C., Jr.; Ji, H.F. A search for medications to treat COVID-19 via in silico molecular docking models of the SARS-CoV-2 spike glycoprotein and 3CL protease. *Travel Med. Infect. Dis.* **2020**, *35*, 101646. [[CrossRef](#)] [[PubMed](#)]
13. Elfiky, A.A. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. *Life Sci.* **2020**, *253*, 117592. [[CrossRef](#)] [[PubMed](#)]
14. Wang, M.; Cao, R.; Zhang, L.; Yang, X.; Liu, J.; Xu, M.; Shi, Z.; Hu, Z.; Zhong, W.; Xiao, G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* **2020**, *30*, 269–271. [[CrossRef](#)] [[PubMed](#)]

15. Liu, J.; Cao, R.; Xu, M.; Wang, X.; Zhang, H.; Hu, H.; Li, Y.; Hu, Z.; Zhong, W.; Wang, M. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Dis.* **2020**, *6*, 16. [[CrossRef](#)] [[PubMed](#)]
16. Gao, J.; Tian, Z.; Yang, X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience Trends* **2020**, *14*, 72–73. [[CrossRef](#)]
17. Colson, P.; Rolain, J.-M.; Raoult, D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *Int. J. Antimicrob. Agents* **2020**, *55*, 105923. [[CrossRef](#)]
18. Gotz, V.; Magar, L.; Dornfeld, D.; Giese, S.; Pohlmann, A.; Höper, D.; Kong, B.W.; Jans, D.A.; Beer, M.; Haller, O.; et al. Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Sci. Rep.* **2016**, *6*, 1–15.
19. Wagstaff, K.; Sivakumaran, H.; Heaton, S.; Harrich, D.; Jans, D. Ivermectin is a specific inhibitor of importin  $\alpha/\beta$ -mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem. J.* **2012**, *443*, 851–856. [[CrossRef](#)]
20. Tay, M.Y.F.; Fraser, J.E.; Chan, W.K.K.; Moreland, N.J.; Rathore, A.P.; Wang, C.; Vasudevan, S.G.; Jans, D.A. Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. *Antivir. Res.* **2013**, *99*, 301–306. [[CrossRef](#)]
21. Yang, S.N.Y.; Atkinson, S.C.; Wang, C.; Lee, A.; Bogoyevitch, M.A.; Borg, N.A.; Jans, D.A. The broad spectrum antiviral ivermectin targets the host nuclear transport importin  $\alpha/\beta$ 1 heterodimer. *Antivir. Res.* **2020**, *177*, 104760. [[CrossRef](#)]
22. Lundberg, L.; Pinkham, C.; Baer, A.; Amaya, M.; Narayanan, A.; Wagstaff, K.M.; Jans, D.A.; Kehn-Hall, K. Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication. *Antivir. Res.* **2013**, *100*, 662–672. [[CrossRef](#)]
23. Caly, L.; Druce, J.D.; Catton, M.G.; Jans, D.A.; Wagstaff, K.M. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antivir. Res.* **2020**, *178*, 104787. [[CrossRef](#)]
24. Fisher, M.H.; Mrozik, H. Ivermectin and abamectin. In *Chemistry*; Campbell, W.C., Ed.; Springer: New York, NY, USA, 1989; pp. 1–23.
25. González-Canga, A.; Sahagún-Prieto, A.M.; Diez-Liébana, M.J.; Martínez, N.F.; Vega, M.S.; Vieitez, J.J.G. The pharmacokinetics and interactions of ivermectin in humans—A mini review. *AAPS J.* **2008**, *10*, 42–46. [[CrossRef](#)] [[PubMed](#)]
26. Nicolas, P.; Maia, M.F.; Bassat, Q.; Kobylinski, K.C.; Monteiro, W.; Rabinovch, N.R.; Menéndez, C.; Bardají, A.; Chaccour, C. Safety of oral ivermectin during pregnancy: A systematic review and meta-analysis. *Lancet Glob Health* **2020**, *8*, e92–e100. [[CrossRef](#)]
27. Edwards, G.; Dingsdale, A.; Helsby, N.; Orme, M.L.; Breckenridge, A. The relative systematic availability of ivermectin after administration as capsule, tablet, and oral solution. *Eur. J. Clin. Pharmacol.* **1988**, *35*, 681–684. [[CrossRef](#)] [[PubMed](#)]
28. Whitworth, J.A.; Hay, C.R.; McNicholas, A.M.; Morgan, D.; Maude, G.H.; Taylor, D.W. Coagulation abnormalities and ivermectin. *Ann. Trop. Med. Parasitol.* **1992**, *86*, 301–305. [[CrossRef](#)] [[PubMed](#)]
29. Lv, C.; Liu, W.; Wang, B.; Dang, R.; Qiu, L.; Ren, J.; Yan, C.; Yang, Z.; Wang, X. Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo. *Antivir. Res.* **2018**, *159*, 55–62. [[CrossRef](#)]
30. Tu, Y.F.; Chien, C.S.; Yarmishyn, A.A.; Lin, Y.Y.; Luo, Y.H.; Lin, Y.T.; Lai, W.Y.; Yang, D.M.; Chou, S.J.; Yang, Y.P. A review on SARS-CoV-2 and the ongoing clinical trials. *Int. J. Mol. Sci.* **2020**, *21*, 2657. [[CrossRef](#)]
31. Caly, L.; Wagstaff, K.M.; Jans, D.A. Nuclear trafficking of proteins from RNA viruses: Potential target for antivirals? *Antivir. Res.* **2012**, *95*, 202–206. [[CrossRef](#)]
32. Jans, D.A.; Martin, A.J.; Wagstaff, K.M. Inhibitors of nuclear transport. *Curr. Opin.* **2019**, *58*, 50–60. [[CrossRef](#)] [[PubMed](#)]
33. Timani, K.A.; Liao, Q.; Ye, L.; Zeng, Y.; Liu, J.; Zheng, Y.; Ye, L.; Yang, X.; Lingbao, K.; Gao, J.; et al. Nuclear/nucleolar localization properties of C-terminal nucleocapsid protein of SARS coronavirus. *Virus Res.* **2005**, *114*, 23–34. [[CrossRef](#)] [[PubMed](#)]
34. Frieman, M.; Yount, B.; Heise, M.; Kopecky-Bromberg, S.A.; Palese, P.; Baric, R.S. Severe acute respiratory syndrome coronavirus ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum/Golgi membrane. *J. Virol.* **2007**, *81*, 9812–9824. [[CrossRef](#)] [[PubMed](#)]

35. FDA Letter to Stakeholders: Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans. Available online: <https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans> (accessed on 1 June 2020).
36. Patri, A.; Fabbrocini, G. Hydroxychloroquine and ivermectin: A synergistic combination for COVID-19 chemoprophylaxis and treatment? *J. Am. Acad. Dermatol.* **2020**, *82*, e221. [[CrossRef](#)]
37. Momekov, G.; Momekova, D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view. *MedRxiv* **2020**, *34*, 469–474.
38. Cavalcanti, A.B.; Zampieri, F.G.; Rosa, R.G.; Azevedo, L.C.P.; Veiga, V.C.; Avezum, A.; Damiani, L.P.; Marcadenti, A.; Kawano-Dourado, L.; Lisboa, T. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N. Engl. J. Med.* **2020**. [[CrossRef](#)]
39. Liu, Y.; Gayle, A.; Wilder-Smith, A.J.R. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J. Travel Med.* **2020**. [[CrossRef](#)]
40. Frediansyah, A.; Tiwaric, R.; Sharun, K.; Dhama, K.; Harapan, H. Antivirals for COVID-19: A critical review. *Clin. Epidemiol. Glob Health* **2020**. (In press) [[CrossRef](#)]



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).