Therapeutic potential of ivermectin for COVID-19

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Abstract

Background The aim of the present theoretical essay is to evaluate evidence published on the characteristics of the transcription of SARS-CoV-2 and explain the mechanism of action of ivermectin that may justify its therapeutic use in clinical practice for the treatment of COVID-19. Methods Laboratory studies, narratives, editorials and expert opinions on the subject were identified through a systematic search of the literature in the Medline/PubMed, Cochrane Library, Web of Science and Embase databases. Two blinded, independent reviewers selected studies published up to May 17, 2020 based on the eligibility criteria. Results The search of the databases led to the retrieval of 25 articles. After the different phases of the selection process, eight articles were included in the present review for the extraction of relevant data. The results suggest that ivermectin inhibits the viral replication of SARS-CoV-2 through the action of the hypoxia-inducible factor (HIF-1α) and consequent destabilization of importin α/β1 proteins. Conclusions Ivermectin inhibits the viral replication of SARS-CoV-2. Laboratory and clinical studies are needed to provide more evidence in terms of the best posology and possible associations with other drugs for combatting COVID-19.

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BRIEF DESCRIPTION

What is already known about this subject

We already know how some viruses replicate, as well as the mechanism of action of drugs with antiviral potential, such as ivermectin. Its therapeutic potential against SARS-CoV-2 is related to the inhibition or under-regulation of importin α/β1 complex, which results in the control of replication of single-stranded viral

RNA in the cell nucleus. The antiviral potential of ivermectin can be enhanced by micronutrients, especially zinc.

What this study adds

This study adds the participation of the hypoxia-inducible factor (HIF-1α) in the antiviral mechanism of action of ivermectin, in addition to responding to reductions in the oxygen available in the cellular environment (common in cases of severe acute respiratory syndrome such as COVID-19). Its modulation can affect viral replication and the cytokine-mediated proinflammatory response, through genetic underexpression in the host cell nucleus. In addition to contributing to a better antiviral response to ivermectin by modulating the importin α/β1-HIF-1α complex, zinc promotes a beneficial immunomodulation for the patient, by reducing the regulation of pro-inflammatory cytokines; Ivermectin + zinc represents a potential therapeutic protocol against COVID-19 to be tested at different stages of the disease.

ABSTRACT

Background

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Methods

Laboratory studies, narratives, editorials and expert opinions on the subject were identified through a systematic search of the literature in the Medline/PubMed, Cochrane Library, Web of Science and Embase databases. Two blinded, independent reviewers selected studies published up to May 17, 2020 based on the eligibility criteria.

Results

The search of the databases led to the retrieval of 25 articles. After the different phases of the selection process, eight articles were included in the present review for the extraction of relevant data. The results suggest that ivermectin inhibits the viral replication of SARS-CoV-2 through the action of the hypoxia-inducible factor (HIF-1α) and consequent destabilization of importin α/β1 proteins.

Conclusions

Ivermectin inhibits the viral replication of SARS-CoV-2. Laboratory and clinical studies are needed to provide more evidence in terms of the best posology and possible associations with other drugs for combatting COVID-19.

Keywords: Ivermectin; Coronavirus Infection; Drug Treatment.

INTRODUCTION

The new coronavirus (COVID-19), which is also denominated SARS-CoV-2, causes a novel respiratory disease of a viral origin. On December 8th, 2019, the first reports came out of China of patients with severe cases of pneumonia of an unknown origin, but it was only on January 7th, 2020 that COVID-19 was identified by the Chinese Center of Disease Prevention and Control. According to the World Health Organization (WHO), COVID-19 is a public health emergency affecting hundreds of thousands of people throughout the world [1,2].

No vaccine or specific treatment is yet defined for this new coronavirus and there is an urgent need to find a therapeutic resource that can impede or at least control the replication of this virus [3]. Antiviral drugs are being studied to assist in combatting COVID-19, as antivirals inactivate enzymes that activate glycoproteins, thereby impeding the penetration of the virus in human cells [4].

The literature suggests the use of ivermectin as a potential drug for combatting COVID-19. Ivermectin is a broad-spectrum antiparasitic agent used in veterinary medicine and approved by the Food and Drug Administration (FDA) for use in humans [5]. This drug is used for the control of onchocerciasis and filariasis as well as the treatment of mange and lice [6]. Ivermectin has also been evaluated in clinical trials for the control of malaria as well as *in vitro* studies for the control of dengue, yellow fever and the zika virus. Ivermectin has also been demonstrated to inhibit the replication of HIV-1 [7,8]

However, more in-depth knowledge on the mechanism of action of ivermectin is needed to gain a better understanding of its capacity for viral inhibition. SARS-CoV-2 is a positive-chain RNA virus. Due to its pharmacokinetic properties, ivermectin has the capacity to inhibit the bond between a virus and the nuclear transport mediated by importins α/β, demonstrating antiviral activity for various RNA viruses [5].

Moreover, ivermectin is a safe medication with low risk to human health and few adverse effects when used at standard doses. A dose of 150-200 μg/kg is recommended for filarial infection and *S. stercoralis* , up to 400 μg/kg is recommended for infection by *Wuchereria bancrofti* and doses higher than 400 μg/kg are recommended for the control of soil-transmitted helminthiasis and malaria [7]. Caly et al. (2020) [9] recently published an *in vitro* study reporting the activity of ivermectin against SARS-COV-2 in Vero-hSLAM cells at a single dose of 5 μM, resulting in viral inhibition within 48 hours [10,11].

There are no randomized clinical trials in the literature on the use of ivermectin for the prophylactic or therapeutic treatment of COVID-19, which hinders its indication and the clinical decision-making process. Therefore, the aim of the present study was to perform a theoretical essay on the literature to contribute to the study and clarification of the characteristics of the transcription of SARS-CoV-2 and explain the pharmacokinetic mechanism of ivermectin in viral control associated with the new coronavirus.

MATERIALS AND METHODS

Type of study

Systematic, hybrid, theoretical essay.

Eligibility criteria

The following were the inclusion criteria: (1) randomized clinical trials; (2) cohort studies; (3) case-control studies; (4) *in vitro* studies; (5) case reports and case series (8) literature reviews; (9) expert opinions; (10) studies published in English, Spanish and Portuguese; (11) no restriction regarding date or time of publication.

Studies were excluded for the following reasons: (1) failure to evaluate the action of ivermectin for the treatment of COVID-19; (2) other types of treatment for COVID-19; (3) indications for ivermectin other than its use for the current pandemic; (4) studies not related to the subject; (5) studies with incomplete texts available in the databases.

Search strategy

Two authors (K.K.N.G. and A.F.M.V.) performed independent searches of the MEDLINE (via PubMed), Web of Science (via CAPES periodicals), Cochrane Library (via CAPES periodicals) and Embase (via CAPES periodicals) databases for relevant articles published up to May 17$^{\text{th}}$, 2020. No restriction was imposed regarding the date of publication. A reference management software (EndNote Online) was used for the collection of articles and exclusion of duplicates. The following combinations of keywords were used: "COVID-19 AND ivermectin" OR "COVID-19 AND stromectol" OR "COVID-19 AND mectizan" OR "SARS-CoV-2 AND ivermectin" OR "SARS-CoV-2 AND stromectol" OR "SARS-CoV-2 AND mectizan" OR "coronavirus AND ivermectin" OR "coronavirus AND stromectol" OR "coronavirus AND mectizan".

An additional search was performed of the grey literature using the Brazilian Digital Library of Theses and Dissertations and a hand search was performed of relevant journals.

Selection of studies

The selection of studies was conducted in two stages. In the first stage, two authors (K.K.N.G. and A.F.M.V.) performed blinded independent analyses of the titles and abstracts of all references based on the eligibility criteria. A third reviewer (B.C.E.V.) was involved in the consensus meeting when a divergence of opinion arose between the two reviewers regarding the inclusion/exclusion of an article. The level of agreement in this stage was determined using the Kappa statistic. In the second stage, the two reviewers (K.K.N.G. and A.M.F.V.) independently performed the full-text analyses based on the eligibility criteria for the selection of articles to be included in the present review. The included articles were read a second time for the extraction of pertinent data that answered the guiding question and the manuscript was written with the participation of the other authors.

Data extraction

One author (K.K.N.G.) extracted the pertinent information from the articles included in the present review and another author (A.F.M.V.) checked and confirmed the information. The data from the eligibility forms were tabulated. The following information was extracted from each article: authors, year of publication, country in which the study was conducted, type of study, type of drug, dose/posology, verification of viral inhibition through laboratory exams, adverse effects, presence/absence of evaluation of chest radiographs and complications associated with the use of ivermectin for the treatment of COVID-19.

RESULTS

The search of the databases led to the retrieval of 25 articles: nine in MEDLINE, two in Web of Science, one in the Cochrane Library and 13 in Embase. The reference management software (EndNote Online) identified and removed six duplicated articles. The reading of the titles and abstracts resulted in the exclusion of 11 articles. No additional publications were found during the search of the grey literature or scientific journals. Eight articles were submitted to full-text analysis. The flowchart displays the article selection process (Figure 1).

Among the articles included in the present review, Caly et al. (2020) performed the only *in vitro* laboratorial study testing the hypothesis that Vero-hSLAM cells contaminated with SARS-CoV-2 would respond positively to treatment with a single dose of 5 μM of ivermectin. The data were evaluated 0 to 3 days after contamination using reverse transcription analysis followed by real-time polymerase chain reaction (RT-PCR) analysis. The authors report a 93% reducing in viral replication in the first 24 hours and approximately 99.98% in 48 horas, suggesting a 5000-fold reduction in viral RNA within 48 hours in the samples collected. No reduction in viral RNA was found at 72 hours and no toxicity was found at the concentrations tested. The 50% inhibitory concentration (IC50) was approximately 2 μM under these conditions [9].

Schmith, Zhou and Lohmer (2020) performed a mathematical laboratorial study involving simulations of the population pharmacokinetic model to predict the time of total plasma concentration (bound and unbound) after a single administration of 60 mg and repeated 120 mg of the approved dose of ivermectin (200 μg/kg). The simulations were performed using the NONMEM program, version 7.4 (ICON Development Solutions, Ellicott City, MD). The total plasma concentration time was simulated to predict exposure to the approved dose of ivermectin (200 μg/kg in increments of 3 mg) and 120 mg in single doses. A dose of 60 mg administered three times per week was also simulated. According to the authors, total plasma concentrations did not reach the IC50 even when doses tenfold higher than the approved dose were used and predicted lung concentrations would be 1/1 of the IC50 after 60 mg three times per week or after 120 mg once per week [11].

The narrative review performed by Yavuz and Ünal (2020) involved 300 ongoing clinical trials using antiviral (including ivermectin) and immunomodulating therapy for COVID-19 [8]. The narrative review by Choudhary and Sharma (2020) addressed ivermectin, hydroxychloroquine and azithromycin used alone or in combinations due to the capacity to inhibit the nuclear importation of viral and host proteins as well as the similar action of hydroxychloroquine and azithromycin, taking into consideration the potential side effects that may be associated with hydroxychloroquine [12]. Confirming the other narrative studies included in the present theoretical essay, Kelleni (2020) lent support to the antiviral study, citing the importance of knowledge regarding IFN-γ, IFN-α-1 and IFN-β in the presence of SARS-CoV-2 [13].

The study by Patrí and Fabbrocini (2020), included in this literary essay, is an editorial study and expert opinion that suggests synergy between ivermectin and hydroxychloroquine (HCQ) [14]. HCQ is believed to serve as an initial barrier, impeding the entrance of the virus in the host cell, and ivermectin is believed to reduce viral replication if the virus enters the cell.

The two last studies included in this review are by Chaccour et al. (2020) and Bray et al. (2020) [7,10] and are editorials and expert opinions on the use of ivermectin for COVID-19, addressing the high doses used in the *in vitro* study by Caly et al. (2020) [9] and highlighting neurotoxicity as a possible side effect.

None of the eight studies included in this review cited the importance of the evaluation of imaging exams, such as chest radiographs, or the possible future complications of the use of ivermectin as treatment for COVID-19. Table 1 summarizes the qualitative data of the studies included in the present systematic review.

DISCUSSION

Avermectin-producing microorganisms were first discovered by the researcher Ōmura in Japan in 1973. Samples of these germs were sent to William Campbell's laboratory in 1974 and evaluated using special screening for anthelmintics. In 1975, the bacterium *Streptomyces avermitilis* was discovered and the family of avermectins was named. Ivermectin belongs to this class and is considered the safest and more effective drug of the group. However, it was only sold in 1981 for veterinary and agricultural use. In 1987, it was registered as a potential drug for use on humans under the brand name Mectizan [5,15].

Ivermectin is a broad-spectrum antiparasitic agent used in the treatment of tropical diseases, such as onchocerciasis, lymphatic filariasis, strongyloidiasis and lice. There is also evidence of its effectiveness for the management of myiasis, trichinosis, malaria, leishmaniasis, trypanosomiasis, Chagas disease and schistosomiasis as well as bed bugs, inflammatory skin lesions, epilepsy, neurological diseases, tuberculosis and some cancers [5].

Curiously, ivermectin also exhibits antiviral activity, inhibiting the replication of some RNA viruses *in vitro* , such as yellow fever and zika virus, although the mechanism of action in the latter case is not clarified, as the study was conducted on mice and had certain limitations [7,9]. Moreover, a phase III clinical study conducted in Thailand (2014-2017) states that ivermectin affects the dengue virus, reporting that a single daily dose resulted in a significant reduction in the concentration of serum levels of the NS1 viral proteins; however, no change in the viremia was found and there was no clinical benefit [8].

Yavuz and Ünal (2020) describe the participation of ivermectin in the inhibition of the replication of HIV by the bond with importin 1 and suggest that the majority of patients with COVID-19 have mild symptoms and do not need any antiviral therapy [8]. However, the authors state that when the administration of this medication is necessary, it is more likely to provide benefits if initiated in the early phase of the disease, when the symptoms can still be modified. Consolidating the mechanism of HIV, Ferreira, Riffel and Sant'Ana (2010) suggest that the therapeutic management of this disease basically consists of the use of specific inhibitors of the viral replication cycle, which effectively reduce the viral burden to undetectable levels for a long period [16].

Coronaviruses belongs to the subfamily Coronavirinae of the family Coronaviridae and the order Nidovirales and are grouped into four types: α-, β-, γ- and δ-CoVs. Six groups of coronaviruses were once known to causes illness in humans: two α-Cov groups and four β-Cov groups [18]. SARS-CoV-2 belongs to the β-Cov group and is the seventh group in this family of coronaviruses, resembling microorganisms that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). According to Zyu et al. (2020), the diagnosis of the disease was assisted by the discovery of the SARS-CoV-2 genome, with the detection of viral RNA using RT-PCR [1].

SARS-CoV-2 can be classified as type IV (positive chain RNA virus) and involves seven phases, such as binding, penetration, coating, transcription and translation, replication, maturation and release of infectious proteins. The SARS-CoV-2 genomic RNA acts as a messenger RNA translated by the host cell's cytoplasmic ribosome.

Studying treatment for HIV-1 and dengue, Wagstaff et al. (2012) described the importance of the movement of proteins between the cytoplasm and nucleus mediated by the superfamily of importin proteins (IMP α/β1) for viral and neoplastic diseases. In this cell culture study, the viral inhibition of the nuclear transport occurred due to the action of ivermectin, demonstrating a broad spectrum in the inhibition of the transduction of cytoplasm-nucleus proteins. The authors concluded that ivermectin is a viable target for the development of urgent antiviral therapies to combat various diseases [19].

Kosyna et al. (2015) performed laboratory tests with and without ivermectin to examine whether the properties of the bond between hypoxia-inducible factor (HIF-1α) and IMP α/β1 and between HIF-1 and nuclear localization signals are affected by the hypoxia mechanism on the cellular level, as HIF-1α can lead to cell decompensation or death, which implies greater pathogenesis by microbial agents. The authors found that ivermectin inhibited both IMP α/β1 and HIF-1α, suggesting its use as treatment for COVID-19. The inflammatory response (proinflammatory cytokines) is exacerbated in patients with severe cases of the disease, which is likely explained by HIF-1α due to its activation by the virus, inducing an inflammatory reaction if no drug is administered to inhibit this factor [20].

Crump et al. (2017) state that ivermectin plays an important role as a potent broad-spectrum inhibitor of nuclear transport mediated by importins α/β and has antiviral activity against several RNA viruses, blocking the nuclear transport of viral proteins [5].

Caly et al. (2020) recently reported the inhibitory effect of ivermectin on the viral activity of SARS-CoV-2. The mechanism of action is similar to those proposed previously, suggesting that SARS-CoV-2 proteins play an essential role in IMP α/β-1 on the intracellular level [9].

For a better understanding, the authors of the present theoretical essay are in agreement with Caly et al. (2020), reporting the mechanism of action of the IMP α/β1 proteins upon bonding to the protein of the coronavirus [9]. IMPα bonds to the nuclear localization signal of the protein to be imported to the nucleus of the host cell. IMP β1 assists in anchoring the importin protein to the nuclear pore complex (NPC), translocating the ternary complex (viral protein and IMP α/β1) to the nucleus of the host cell. Thus, the dissociation of the ternary complex occurs in the nucleus of the host cell and the viral DNA unites with the human DNA, undergoing successive mitoses, releasing viral proteins and infecting other healthy cells. At this point, ivermectin bonds to and destabilizes IMP α/β1, impeding the viral protein of the coronavirus from bonding to importins and consequently impeding the passage of the virus through the NPC to the nucleus of the host cell, thereby inhibiting viral replication (Figure 2).

The urgent search for effective treatment for SARS-CoV-2 is necessary. Patrí and Fabbrocini (2020) suggest the combination of ivermectin and hydroxychloroquine, raising the hypothesis that both medications may work in a synergic manner, with hydroxychloroquine serving as a first-level barrier inhibiting the penetration of the virus through the membrane of the host cells, whereas ivermectin would reduce viral replication [14]. However, there are no clinical studies to prove the beneficial effects of this combination and one must bear in mind the possible adverse reactions associated with hydroxychloroquine. Moreover, Geleris et al. (2020) conducted an observational study involving 1446 patients hospitalized with COVID-19 and found that treatment with hydroxychloroquine was not associated with a reduction in the risk of intubation or death [21].

To provide further scientific evidence of the use of ivermectin on SARS-CoV-2, Caly et al. (2020) preformed an *in vitro* study evaluating Vero-hSLAM cells contaminated with COVID-19 [9]. Two hours after contamination, a single dose of 5 μM of ivermectin was administered, resulting in an approximately 5000-fold reduction in viral RNA in samples collected in the first 48 hours. The authors performed additional studies with serial dilutions, suggesting that the IC50 was 2 μM under these conditions. Schmith, Zhou and Lohmer (2020) discuss these results, suggesting that the concentration of 2 μM resulting in 50% inhibition (IC50) was 35-fold higher than the maximum plasma concentration (Cmax) following the oral administration of the approved dose of ivermectin when administered after fasting. The authors performed population pharmacokinetic simulations after a single administration and repeated administration after fasting of the approved

dose of ivermectine (200 μg/kg) of 60 mg and 120 mg to estimate the doses of ivermectin that would be necessary to result in the IC50 in the lungs of humans. They concluded that plasma concentrations of ivermectin at the total concentration (bound and unbound) did not achieve the IC50 even with a dose 10 times higher than the approved dose and it is unlikely for ivermectin to achieve IC50 in the lungs after a single administration of the approved dose (predicted concentration in lungs: 0.0873 μM) or ten times higher than the approved dose when administered orally (predicted concentration in lungs: 0.820 μM) [11].

Ivermectin is considered a safe medication with few side effects. However, there are reports of encephalitis associated with this drug when used in patients infected by loaiasis (infection caused by the *Loa loa* larvae in the organism, which generally affects the ocular system) [6]. There are also studies that report side effects related to the use of ivermectin for SARS-CoV-2.

Considering *in vitro* laboratory studies, narrative reviews and expert opinions on the subject, we believe that the use of ivermectin is a therapeutic possibility, especially in the early stage of the disease. However, COVID-19 has demonstrated considerable epidemiological differences with regards to age, different countries and patients with comorbidities. It is necessary to evaluate the course of the disease with the purpose of using combined medications, such as the possibility of secondary infections (azithromycin) and other clinical conditions that may occur. Randomized clinical trials are needed with a large number of patients and standardizing the clinical, laboratorial and imaging evaluations and associated medicinal therapy, such as the use of vitamins and zinc as an antiviral agent [22]. Moreover, it is not yet clear whether severe cases of COVID-19 are directly related to viral burden and an exacerbated immune response, directly affecting target organs, such as lung tissue, the myocardium, etc. In this time of conflicting scientific evidence, the clinical conduct should be determined on a case-by-case basis depending on the clinical status of individuals affected by COVID-19. From the financial standpoint, ivermectin is inexpensive and its doses for other purposes have well-established protocols. Moreover, this drug has few side effects.

CONCLUSION

Ivermectin has potential regarding the inhibition of the viral replication of COVID-19 on the cellular level through the hypoxia-inducible factor and importins α/β1. Further experimental, laboratory and clinical studies are needed to provide more evidence of its use as an antiviral agent in contaminated patients.

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Authors contribution: i) Kalyne Kelly Negromonte Gonçalves and Amanda Freire de Melo Vasconcelos contributed to independent searches of the MEDLINE (via PubMed), Web of Science (via CAPES periodicals), Cochrane Library (via CAPES periodicals) and Embase (via CAPES periodicals) databases for relevant articles published up to May 17th, 2020; ii) Davi da Silva Barbirato holds a Ph.D. in Biological Sciences and a postdoctoral fellow in Oral and Maxillofacial Surgery, and contributed to the study design and the establishment of the biological (cellular) mechanisms involved; iii) César Freire de Melo Vasconcelos (Ph.D. student) is a thoracic surgeon and intensivist with experience in the treatment of in-hospital and in-ICU patients with moderate to severe COVID-19, and contributed to the clinical interpretation of the main findings and the writing of the manuscript; and iv) Belmiro Cavalcanti do Egito Vasconcelos (Ph.D.) is a Bucco Maxillofacial Surgeon with extensive experience in the treatment of emergency cases of trauma, pathologies and infections of the oral and maxillofacial region at a referral hospital for trauma and COVID-19 in the State of Pernambuco, Brazil. Professor Vasconcelos coordinated the entire research process and contributed to the clinical interpretation of the main findings. All authors held a consensus meeting to finalize the manuscript.

COMPETING INTERESTS

The authors have no conflict of interest to declare.

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ETHICAL APPROVAL

Not applicable.

PATIENT CONSENT

Not applicable.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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Figure 1 – Flowchart of article selection process.

Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

Table 1 – Characteristics of qualitative studies included in present review.

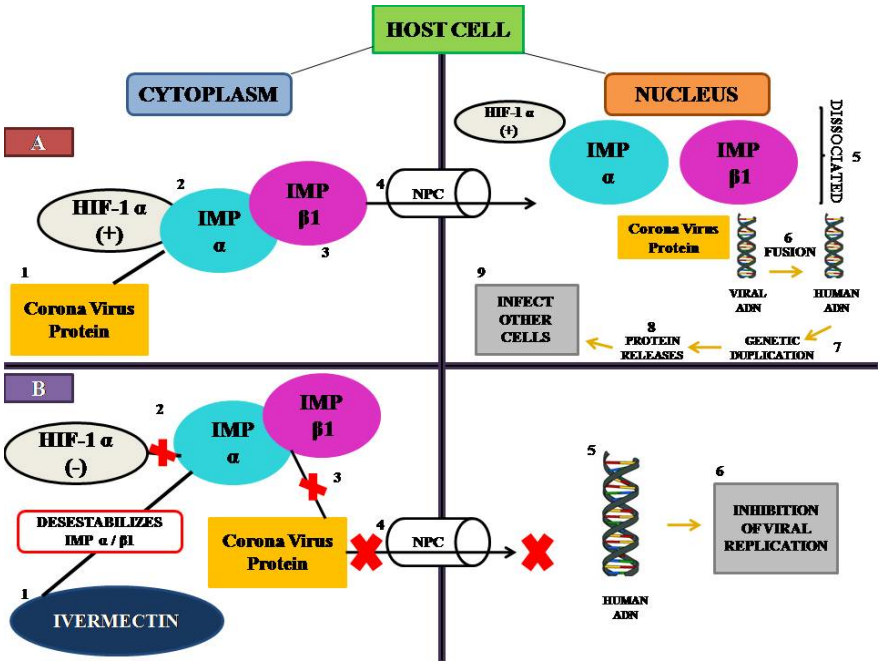
Author/Year/Country	Type of Study	Type of Drug	Dose/Posology	Primary Outcome (viral inhibition) Laboratory exams RT-PCR, Lymphocytes (TCD4, TCD8), Creatinine, Urea, Cytokines (IL6, IL10, TNF alpha), Dimer-D and Highly Sensitive CrP	Secondary Outcome (side effects)	Tertiary Outcome (Evaluation of chest x-ray)	Complicatio
Caly et al., 2020/Australia	Laboratory study (*in vitro*)	Ivermectin	Single dose 5 µM	Viral inhibition 93% in 24 horas, 99.98% in 48 hours and 0% at 72 hours, RT-PCR	Absent	Not applicable	Not applicable
Schmith et al., 2020/USA	Mathematical Laboratory Study	Ivermectin	60 mg 3 x per week or 120 mg 1 x per week	Viral inhibition estimated in lung concentration	Not applicable	Not applicable	Not applicable
Yavuz and Ünal, 2020/Turkey	Narrative study	Ivermectin	Not reported	Absence of nuclear importation between host and virus due to inhibition of IMP 1 protein	Not reported	Not reported	Not reported

Author/Year/Country	Type of Study	Type of Drug	Dose/Posology	Primary Outcome (viral inhibition) Laboratory exams RT-PCR, Lymphocytes (TCD4, TCD8), Creatinine, Urea, Cytokines (IL6, IL10, TNF alpha), Dimer-D and Highly Sensitive CrP	Secondary Outcome (side effects)	Tertiary Outcome (Evaluation of chest x-ray)	Complicatio
Choudhary and Sharma, 2020/India	Narrative study	Ivermectin, HCQ and/or azithromycin	Not reported	Proposes use of ivermectin, HCQ and azithromycin alone or in combination for COVID-19	Not reported	Not reported	Not reported
Kelleni, 2020/Egypt	Narrative study	Ivermectin	Not reported	Proposes study of IFN-γ, IFN α-1 and IFN-β in COVID-19	Not reported	Not reported	Not reported
Patrí and Fabbrocini, 2020/Italy	Editorial, expert opinion	Ivermectin + HCQ	Not reported	Inhibition of nuclear transportation mediated by IMP α/β. Also suggests combining with HCQ to act in synergistic manner	Ivermectin – no severe side effects HCQ – safe if monitored adequately	Not reported	Not reported

Author/Year/Country	Type of Study	Type of Drug	Dose/Posology	Primary Outcome (viral inhibition) Laboratory exams RT-PCR, Lymphocytes (TCD4, TCD8), Creatinine, Urea, Cytokines (IL6, IL10, TNF alpha), Dimer-D and Highly Sensitive CrP	Secondary Outcome (side effects)	Tertiary Outcome (Evaluation of chest x-ray)	Complication
Chaccour et al., 2020/Spain	Editorial, expert opinion	Ivermectin	Not reported	Discusses high doses of ivermectin cited by Caly et al., 2020	Suggests neurotoxicity	Not reported	Not reported
Bray et al., 2020/USA and Brazil	Editorial, expert opinion	Ivermectin	Not reported	Discusses high doses of ivermectin cited by Caly et al., 2020	Not reported	Not reported	Not reported

Legend: RT-PCR, real time polymerase chain reaction; IL, interleukin; CrP, C-reactive protein HCQ, hydroxychloroquine; IFN, interferon; IMP, importin.

Figure 2 – Mechanism of action of coronavirus and viral inhibition by ivermectin. A , IMP alpha has function of bonding to nuclear localization signal of protein to be imported to nucleus of host cell. IMP β1 assists in anchoring importin protein of nuclear pore complex (NPC), translocating ternary complex (viral protein and IMP α/β1) to nucleus of host cell, resulting in dissociation of ternary complex in nucleus of host cell and viral DNA uniting with human DNA, undergoing successive mitoses, releasing viral proteins and infecting other healthy cells; and **B** , action of ivermectin bonding to and destabilizing IMP α/β1, impeding viral protein of COVID-19 from bonding to importins and activating hypoxia-inducible factor (HIF-1α), consequently impeding passage of virus through nuclear pore complex (NPC) to nucleus of host cell, thereby inhibiting viral replication.



Source: Produced by authors.

CAPTIONS FOR ILLUSTRATIONS

Figure 1. PRISMA Flow-Diagram of Literature Review.

Figure 2. Proposed mechanism of action of ivermectin in COVID-19.

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