

Review

From hydroxychloroquine to ivermectin: what are the anti-viral properties of anti-parasitic drugs to combat SARS-CoV-2?

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Abstract

Background: Nearly a year into the COVID-19 pandemic, we still lack effective anti-SARS-CoV-2 drugs with substantial impact on mortality rates except for dexamethasone. As the search for effective antiviral agents continues, we aimed to review data on the potential of repurposing antiparasitic drugs against viruses in general, with an emphasis on coronaviruses.

Methods: We performed a review by screening *in vitro* and *in vivo* studies that assessed the antiviral activity of several antiparasitic agents: chloroquine, hydroxychloroquine (HCQ), mefloquine, artemisinins, ivermectin, nitazoxanide (NTZ), niclosamide, atovaquone and albendazole.

Results: For HCQ and chloroquine we found ample *in vitro* evidence of antiviral activity. Cohort studies that assessed the use of HCQ for COVID-19 reported conflicting results, but randomized controlled trials (RCTs) demonstrated no effect on mortality rates and no substantial clinical benefits of HCQ used either for prevention or treatment of COVID-19. We found two clinical studies of artemisinins and two studies of NTZ for treatment of viruses other than COVID-19, all of which showed mixed results. Ivermectin was evaluated in one RCT and few observational studies, demonstrating conflicting results. As the level of evidence of these data is low, the efficacy of ivermectin against COVID-19 remains to be proven. For chloroquine, HCQ, mefloquine, artemisinins, ivermectin, NTZ and niclosamide, we found *in vitro* studies showing some effects against a wide array of viruses. We found no relevant studies for atovaquone and albendazole.

Conclusions: As the search for an effective drug active against SARS-CoV-2 continues, we argue that pre-clinical research of possible antiviral effects of compounds that could have antiviral activity should be conducted. Clinical studies should be conducted when sufficient *in vitro* evidence exists, and drugs should be introduced into widespread clinical use only after being rigorously tested in RCTs. Such a search may prove beneficial in this pandemic or in outbreaks yet to come.

Key words: Chloroquine, artemisinins, nitazoxanide, COVID-19, corona, SARS, viruses

Table 1. Articles screened, reviewed and included in the review

Drug ^a	Total abstract screened	In vitro and animal model studies included	In vivo studies included
Chloroquine and HCQ	1191	10	21
Artemisinins	116	14	2
Mefloquine	78	3	0
Ivermectin	93	7	5
NTZ	88	14	3
Niclosamide	72	17	0

^aNo articles were found for albendazole and atovaquone.

Introduction

The COVID-19 pandemic has already incurred a shocking price in terms of lives lost, worldwide economic recession, political tensions and psychological stress.^{1,2} This pandemic's effects on high-risk populations are still being studied.³ Since time is critical, and no treatment except dexamethasone has been proven to decrease mortality,⁴ there is now a worldwide rush to find an effective antiviral agent.

Repurposing of existing antivirals is ongoing but results from most studies thus far have been poor, with many agents showing promise in small groups of relatively young patients, who are less likely to succumb to COVID-19. The few controlled trials that have been performed are somewhat disappointing; the protease inhibitor lopinavir/ritonavir has failed to demonstrate clear superiority over a placebo in one randomized controlled trial (RCT). A combination of lopinavir, ritonavir, ribavirin and interferon beta-1b was found to be effective in alleviating symptoms and shortening viral shedding, but such complex regimen is unlikely to become a mainstay of treatment.⁵

Another antiviral compound, remdesivir, was initially shown to be modestly effective in shortening illness duration in an RCT.⁶ However, recent clinical trials including the World Health Organization solitary trail (that did not include a placebo group), did not show any mortality benefits.^{7,8} The drug is administered only intravenously, probably does not decrease mortality and is unavailable to most clinicians worldwide.

Under these circumstances, the use of older antiparasitic agents, based on *in vitro* antiviral activity, animal studies or preliminary data on COVID-19 patients, is an interesting option. In this review, we describe the available evidence on the activity of antiparasitic agents, including antimalarial drugs, on viruses and specifically on SARS-CoV-2 and reviewed interventional and observational studies that assessed the clinical effect of those therapies for COVID-19.

Methods

Type of studies

In this review, we screened *in vivo* and *in vitro* studies that focus on antiviral activities of several antiparasitic agents, including specific activity against COVID-19 and other coronavirus-related infections [Middle East respiratory syndrome (MERS), SARS and SARS-CoV-1]. Antiparasitic agents include HCQ, chloroquine, mefloquine, artemisinins, ivermectin, nitazoxanide (NTZ) and niclosamide, atovaquone and albendazole. The structures and uses of these drugs are given in Table 2. We included

studies published during the COVID-19 pandemic in English. We have included RCTs, non-randomized comparative cohorts, case series and case reports containing data on the antiviral activity of individual drugs. *In vitro* studies were included if detailing an experiment with a relevant drug and a specific virus.

Types of outcome measures

Clinically relevant outcomes such as mortality rates, hospital admission rates, lengths of hospital stay and disease severity were recorded. In addition, virologic parameters such as viral clearance time, viral shedding duration and viral load when relevant were also described.

Search methods for identification of studies

We conducted a systematic electronic literature screen using the PubMed search engine by searching one or more of the following terms: 'COVID', 'MERS', 'SARS' or 'antiviral', combined with the names of several antiparasitic agents (chloroquine, HCQ, mefloquine, artemisinins, NTZ, niclosamide, ivermectin, albendazole and atovaquone). We used references of retrieved papers, including reviews or systematic reviews to identify further studies. Two reviewers independently screened all studies published before 15 November 2020. We excluded all retrieved articles that did not fulfil the inclusion criteria. In cases of disagreement, a third reviewer acted as arbitrator.

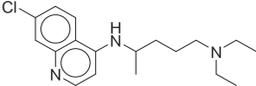
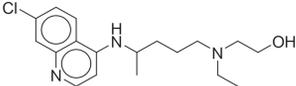
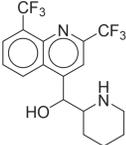
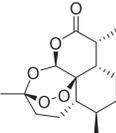
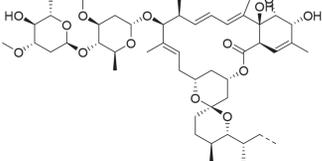
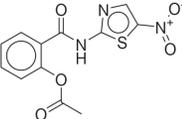
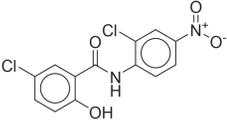
Results

The numbers of all *in vitro* and *in vivo* articles that were included are shown in Table 1. Our main findings are summarized in Tables 2 and 3. As we found neither *in vitro* nor *in vivo* studies for albendazole or atovaquone, these two agents are not included in this review.

Chloroquine and HCQ

Chloroquine and HCQ are 4-aminoquinoline organic compounds that have long been used for the treatment and prevention of malaria, as antibacterial therapy for Q fever and as immune modulators. These two drugs are very similar in structure, and their mechanism of action appears identical. HCQ is well tolerated and is generally regarded to have a better safety profile than chloroquine.

Table 2. Mechanism of action of antiparasitic drugs when used as antiviral agents

Drug name	Chemical structure	Pathogen for which the drug is indicated (reference)	Proposed Antiviral Mechanism of action
Chloroquine		<i>Plasmodium spp.</i>	Prevents viral entry, transport and post-entry events. It is a weak base that increases the pH of low-pH organelles, such as endosomes, Golgi vesicles, and lysosomes; suppressing the production and release of TNF α and interleukin 6, which mediate the inflammatory complications of several viral diseases. ^{13,24,102}
HCQ		<i>Plasmodium spp., Coxiella burnetii</i>	Same as chloroquine
Mefloquine		<i>Plasmodium spp.</i>	Inhibits viral DNA replication in cells after viral entry ⁶⁹
Artesiminins		<i>Plasmodium spp., Schistosoma spp.</i>	Reduce virus DNA binding activity of NF- κ B and Sp1, ⁵⁵ affect viral replication ²⁵
Ivermectin		Helminths and ecto parasites	Inhibits nuclear import of host and viral proteins thereby inhibiting viral replication ⁷⁸
Nitazoxanide		Helminthic and protozoal infections	Blocks the maturation of the viral hemagglutinin at the post-translational stage ⁹²
Nicosamide		Protozoal infections	Neutralize endolysosomal pH and interfere with pH-dependent membrane fusion ¹⁰⁰

Most adverse reactions of HCQ are mild and include gastrointestinal adverse effects, skin rash and photosensitivity. Large cumulative dosages, commonly administered over a prolonged period of time, have been associated with irreversible toxic retinopathy. Cardiac toxicity is rare but may be life threatening.⁹ According to current knowledge, significant QT

prolongation occurs in 3–13% of patients, with increasing incidence with age and among patients that are co-treated with azithromycin. Although torsades de pointes has not been recorded in small cohorts of COVID-19 patients, it is possible that fatal arrhythmias will be encountered if the drug will be used extensively.^{10–12}

Table 3. Activity of selected antiparasitic agents against different coronaviruses

Drug	In-vitro study	Animal Model	Clinical trial	comments
HCQ ^{26,27,30-41,43-49}	SARS-CoV-2	SARS-CoV-2	Conflicting results	Widely used worldwide, conflicting results in observational studies, no benefit in RCTs.
Chloroquine ^{21-25,29}	SARS-CoV-1 SARS-CoV2 MERS-CoV	None	None	None
Artemisinins ⁶⁶⁻⁶⁸	SARS-CoV-1	None	None	<i>In silico</i> study suggests possible activity against SARS-CoV-2
Mefloquine ^{71,72}	Pangolin & Feline coronaviruses	None	None	
Ivermectin ^{34,78,81}	SARS-CoV-2	None	None	Conflicting results. A synergistic effect with HCQ has been suggested.
NTZ ^{23,94-96}	MERS-CoV-1 Canine coronavirus SARS-CoV-2	None	One clinical trial	Benefit unclear
Niclosamide ⁹⁷⁻⁹⁹	SARS-CoV-1, MERS-CoV	None	None	

Chloroquine is active *in vitro* and in animal models against several viruses, including human immunodeficiency virus (HIV),¹³ hepatitis C virus (HCV),¹⁴ influenza type H1N1,¹⁵ H5N1,¹⁶ flaviviruses such as dengue virus and Zika,¹⁷ MERS virus¹⁸⁻²⁰ and SARS-CoV-1.²¹⁻²⁵

In early *in vitro* studies, chloroquine was found effective in blocking SARS-CoV-2 infection at low concentrations.²³ Recent *in vitro* and physiologically based pharmacokinetic modelling studies found higher potency for HCQ compared to chloroquine in reducing SARS-CoV-2.^{26,27}

Clinical experience with HCQ and chloroquine

From the onset of the COVID-19 pandemic, HCQ was administered in most affected countries. A dose of 400 mg twice daily followed by 200 mg twice daily of HCQ was predicted to achieve an antiviral effect based on pharmacokinetic (PK) modelling, although dosage and treatment duration varied between guidelines.²⁷ In the current review, we did not specify the exact doses that were used; we refer the reader to a previous systematic review for more specific details.²⁸

In some non-randomized comparative studies or small cohorts, a shortening of clinical disease, a faster viral clearance and a decrease in the likelihood to develop pneumonia were reported after the use of chloroquine or HCQ.²⁹⁻³² The combination of HCQ and azithromycin was also suggested to be beneficial in non-randomized small non-comparative studies.^{30,33} Possible synergistic effects with ivermectin were also suggested.³⁴

Other observational studies demonstrated no significant reduction in mortality rates after HCQ treatment.³⁵⁻³⁹ In one study, all-cause mortality risk was significantly higher among HCQ-treated patients compared to patients that were not treated with HCQ [adjusted hazard ratio 1.83; 95% confidence interval (CI) 1.16-2.89; $P = 0.009$].⁴⁰

Recently, the results of three large scale RCTs were published. The 'RECOVERY Collaborative group' trial compared 1561 patients treated with HCQ to 3155 patients that received

standard of care. Death within 28 days occurred in 421 patients (27.0%) in the HCQ group compared to 790 (25.0%) in the usual-care group (rate ratio, 1.09; 95% CI, 0.97-1.23; $P = 0.15$). Furthermore, patients in the HCQ group that were not undergoing mechanical ventilation at baseline had a higher frequency of invasive mechanical ventilation or death (30.7 vs 26.9%; risk ratio, 1.14; 95% CI, 1.03-1.27).⁴¹ The WHO solitary study compared 954 patients treated with HCQ to 909 patients receiving its control. Death occurred in 10.9% of patients receiving HCQ and in 9.2% receiving its control (rate ratio, 1.19; 95% CI, 0.89-1.59; $P = 0.23$). The use of HCQ did not reduce initiation of ventilation or hospitalization duration.⁷ The third study evaluated 479 hospitalized adults with respiratory symptoms from COVID-19. It demonstrated no significant differences in the distribution of the Day 14 clinical status score (measured using a 7-category ordinal scale) for patients receiving HCQ compared with placebo [adjusted odds ratio (OR), 1.02].⁴²

Few smaller RCTs were also published. Two of them demonstrated no significant differences in the virological cure rates between HCQ treatment and the standard of care groups.^{43,44} In three others, no mortality and clinical status benefits were observed using HCQ (or HCQ and Azithromycin) compared with standard of care treatment.⁴⁵⁻⁴⁸

One large RCT assessed the role of HCQ in post-exposure prevention of COVID-19. It demonstrated no significant difference in the new cases of COVID-19 between the HCQ treatment (800 mg once, followed by 600 mg in 6-8 hours, then 600 mg daily for 4 additional days) and the placebo groups.⁴⁹

A specific alert cautioning against HCQ use without appropriate monitoring was issued by the Food and Drug Administration (FDA).⁵⁰ Similarly, the WHO recently discontinued the Solidarity Trial citing lack of any benefit of HCQ.⁵¹

Artemisinins

It is produced from the plant *Artemisia annua*; artemisinin and its derivatives have become the main weapon in the fight

against malaria. The antimalarial effect of artemisinins is probably related to the formation of reactive oxygen species, although its full mechanism of action is unknown.⁵² Modulation of heme oxygenase-1 by artesunate has been also suggested as a treatment that lowers mortality and improves sepsis-related lung injury in an animal model.⁵³

The effect of artemisinins when used as antiviral agents has been assessed for several viruses.^{54,55} Artemisinin and artesunate inhibited the viral production of hepatitis B virus and Epstein-Barr virus.⁵⁶ Artemisinins, either alone or synergistically with other antiviral agents, was shown to be active against Cytomegalovirus,^{57–60} inhibited replication of John Cunningham (JC) virus,⁶¹ and BK virus⁶² and has been used anecdotally to treat HHV6 myocarditis.⁶³

There has been one notable demonstration of widespread artemisinin use as an ‘accidental’ antiviral. During the 2014 Ebola epidemic in Liberia, all patients were prescribed either artesunate–amodiaquine or artemether–lumefantrine regimens empirically for suspected co-infection with malaria. Those who were treated with artesunate–amodiaquine had a 31% lower risk of death. This effect was stronger among patients without malaria.^{64,65} This was, however, a non-randomized trial, and unknown confounding factors, such as cases of low-level *Plasmodium* parasitemia that might have been missed, may have biased the results.

A. annua extract exhibited activity against SARS CoV-1 as measured by a cytopathic effect reduction (that does not prove an effect on the virus itself).⁶⁶ In another study, artesunate did not show an inhibitory activity against SARS CoV-1 in a cell line.⁶⁷ A recent *in silico* study showed a potential interaction between artemisinins and the SARS-CoV-2 Spike protein Lys353 and Lys31 binding hotspots, but did not directly assess antiviral activity.⁶⁸ These *in vitro* and *in silico* studies, and the fact that artesunate leads to a decrease in sepsis-related lung injury in an animal model, suggest that artemisinins may prove to be interesting candidates for further testing as anti-COVID-19 agents.⁵³

Mefloquine

Mefloquine is an antimalarial similar in structure to quinine. It is active through the destruction of the asexual forms of the *Plasmodium* parasite. In the past, it has been used for patients with progressive multifocal encephalopathy due to *in vitro* anti-JC virus activity.⁶⁹ A RCT failed to demonstrate any benefit, and its use as an antiviral has been largely abandoned.⁷⁰ *In vitro*, mefloquine demonstrates antiviral activity against coronaviruses, similar to earlier reports with JC virus. In a cell culture, mefloquine inhibits the cytopathic effect of two coronaviruses closely related to SARS CoV-2: the pangolin coronavirus GX_P2V/pangolin/2017/Guangxi and feline coronavirus.^{71,72} To the best of our knowledge, no RCT is currently assessing the possible use of mefloquine for COVID-19.

Ivermectin

Ivermectin is used to treat many parasitic infections such as filariasis, soil-transmitted helminths, scabies and head lice, and

it is relatively safe. The discoverers of ivermectin, its precursor, received the 2015 Nobel Prize for their achievement.⁷³ Its antiparasitic effect involves an increase in parasite cell membrane permeability, a mechanism naturally irrelevant to viruses. It has been shown, however, to display some *in vitro* activity against dengue virus, chikungunya virus and other flaviviruses.^{74–76} One RCT that was conducted in Thailand and published only as an abstract demonstrated shorter duration of NS1 antigenemia in patients with dengue fever; however, it failed to demonstrate any clinical benefit.⁷⁷

In vitro studies suggest that ivermectin leads to a ~5000-fold reduction in SARS-CoV-2 RNA at 48 hours, likely through inhibiting IMP α / β -mediated nuclear import of viral proteins.⁷⁸ It remains unclear, however, if relevant concentrations can be achieved with current human or veterinary drug formulations, and what the *in vivo* effect would be. A synergistic effect of ivermectin and HCQ has also been suggested.³⁴

Recently, few countries in Latin America used ivermectin as a routine, yet unproven, treatment of COVID-19. In northern Bolivia 350 000 doses were given to health care workers and in Peru around 20 000 bottles of animal-grade ivermectin were sold on the black market as a treatment for COVID-19.⁷⁹ A recent RCT evaluated the effect of ivermectin or ivermectin and doxycycline therapy on hospitalized COVID-19 patients. No significant difference in fever, cough or sore throat were observed between placebo and treatment groups after 7 days. Earlier virological clearance was observed in the ivermectin group compared to placebo, but not in the ivermectin and doxycycline group.⁸⁰

A retrospective cohort study demonstrated lower mortality in the ivermectin group compared with the standard of care (15.0 vs 25.2%, OR 0.52, 95% CI 0.29–0.96, $P = 0.03$) and lower mortality of patients with severe pulmonary disease treated with ivermectin (38.8 vs 80.7%, OR 0.15, CI 0.05–0.47, $P = 0.001$), but with no significant differences in the rates of successful weaning from mechanical ventilation (36.1 vs 15.4%, OR 3.11 (0.88–11.00), $P = 0.07$).⁸¹ Other small, non-randomized trials, which are potentially biased, have reported conflicting results regarding the benefit of ivermectin.^{82–84}

As the level of evidence of these data is likely low, the efficacy of ivermectin against COVID-19 remains to be proven. However, based on current evidence, it is unlikely that Ivermectin will be a game changer in COVID-19 treatment.

Nitazoxanide

NTZ is an antiparasitic drug used for the treatment of *Giardia* and *Cryptosporidium* infections, and the research of its possible repurposing for treatment of several viruses is ongoing. These viruses include, among others, parainfluenza, respiratory syncytial virus, canine coronavirus, rhinovirus and flaviviruses, including HCV, hepatitis B virus, HIV and influenza.^{85–90} NTZ has an *in vitro* synergistic effect against influenza A virus when combined with oseltamivir and zanamivir.⁹¹ NTZ acts against influenza viruses by blocking the maturation of the viral hemagglutinin at the post-translational level.⁹² Nitazoxanide, the active circulating metabolite of NTZ, is capable of inhibiting the replication of several strains of influenza A and B-16 strains of influenza A/H1N1, H3N2, H3N2v, H3N8, H5N9, H7N1 and one strain

of influenza B.⁸⁹ In an RCT that included 624 patients with influenza virus infection, NTZ was associated with a reduction in the duration of symptoms compared to a placebo.⁹⁰ In another RCT conducted among patients with acute respiratory illness that required hospital admission in Mexico (6.6% of whom were infected with various coronaviruses), NTZ was not associated with any benefits compared to placebo.⁹³ Patients in this study, however, had multiple causative agents, both bacterial and viral, so the measure of effect of NTZ on specific pathogens was impossible to assess.

NTZ exhibits antiviral activity against MERS-CoV and other coronaviruses by inhibiting the expression of the viral N protein,^{94,95} and inhibits the SARS-CoV-2 at a low-micromolar concentration.²³ One small prospective non-controlled study that assessed NTZ treatment of in and outpatients with COVID-19 was performed. Among 20 women (pregnant or in immediate puerperium) that were treated with NTZ, two women died. Five hospitalized patients showed a positive outcome with two patients weaned from mechanical ventilation. A total of 16 outpatients treated with NTZ were cured.⁹⁶ The low number of patients and the relatively high mortality rate do not support the use of this agent against COVID-19. However, larger studies are needed in order to provide more solid data.

Niclosamide

Niclosamide (2',5-dichloro-4'-nitrosalicylanilide) is another FDA approved drug with anticestodal activity that was discovered in 1958. It has an *in vitro* antiviral effect against a broad range of viruses such as SARS-CoV-1,^{97,98} MERS-CoV,⁹⁹ Zika virus, Japanese encephalitis virus, HIV, HCV and human adenovirus.^{100,101} The broad antiviral activity of niclosamide is attributed to its ability to neutralize endo-lysosomal pH and interfere with pH-dependent membrane fusion, which is an essential step in viral entry mechanisms. The antiviral effect of niclosamide should be further assessed *in vitro* before any consideration of clinical utility could be made.

Discussion

The current COVID-19 pandemic has strained national and international resources. The research community has produced a vast amount of new research. However, efforts were at times fragmented and the methodology of many clinical trials that were performed was of low quality. Several months into the outbreak, the number of large, well-conducted RCTs that have been published is still small, despite the millions of infected people worldwide. The only antiviral drug with proven benefit, remdesivir, has been shown to shorten symptom duration in a large RCT that included >1000 patients. A non-significant trend towards lower mortality rates has been observed in this trial although absolute risk reduction was small in the standard of infectious diseases. Remdesivir is therefore only modestly effective, and the search for more active anti-SARS-CoV-2 continues.⁶

We included in this review several antiparasitic agents that have been shown to have some *in vitro* or *in vivo* antiviral activities. We elaborated on drug activity against different viruses,

including the new SARS-CoV-2 and its suggested mechanisms of action (Tables 2 and 3).

Most drugs in Table 2 were shown to reduce the viral replication stage by affecting cellular organelles. However, intensive *in vitro/in vivo* studies are required to establish the detailed mechanism of action of these agents against viruses, particularly against SARS-CoV-2. Combination therapies of drugs with effects on the various stages of the viral life cycle should be also considered.

The limitations of this review are those of the studies themselves. *In vitro* studies have used very different methodologies, and at least some were authored by researchers with potential conflict of interests. Some clinical studies were limited to small cohorts that were prone to selection bias, i.e. inclusion of patients with relatively good prognosis. The rate of publication of well-conducted RCTs, as mentioned before, has been disappointingly slow, and recent studies have been retracted from major journals due to methodological or ethical issues.

The only antiparasitic agent that has been included in major RCTs is HCQ. Although initial observational trials suggested benefit of HCQ, larger high-quality trials provide ample evidence that HCQ should not be used neither for treatment nor for prevention of COVID-19. Its inclusion in clinical trials using differing protocols is ethical as no excess mortality was shown in the Solidarity trials.¹⁰ We call for the continuation of pre-clinical research of existing compounds with potential antiviral effect against SARS-COV-2. However, as *in vitro* results and virologic tests often correlate poorly with actual efficacy, we argue that drugs should be introduced into widespread clinical use only after being rigorously tested in RCTs. Such a search may prove beneficial in this pandemic, or in future outbreaks yet to come.

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Author statements

All authors have read and approved the contents of this manuscript.

Conflict of interests

None declared.

Author contributions

SR—data collection, literature search and writing of manuscript (MS); AN—study design, data collection and writing of MS; AD—data analysis and writing of MS; NP—data collection and literature search; ES—study design and writing of MS.

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