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A systematic review on Ivermectin

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Abstract

Ivermectin works as genocide on a variety of parasites. Despite being a macrocyclic lactone, nothing is known about its antibacterial activity, maybe as a result of the need for micromolar concentrations to operate therapeutically at the tissue level. Staphylococcus aureus is one of the pathogenic bacteria of significant medical importance that causes a multitude of diseases in a variety of hosts, including both people and animals. It is one of the most pathogenic organisms, according to some. S. aureus is now resistant to the majority of the current medicines due to the advent of methicillin resistance, making treatment even more challenging. Therefore, the need for alternative anti-staphylococcal medicines is urgent.

Keywords: Ivermectin; Bacteria; COVID-19; SARS-CoV-2

1. Introduction

Onchocerciasis, helminthiases, and scabies are just a few of the neglected tropical diseases that are treated using the FDA-approved antiparasitic medication ivermectin.Ivermectin has been used extensively for these purposes and is often tolerated well. The FDA has not given ivermectin approval to treat viral infections of any kind.

Penicillin and aspirin may have had the biggest positive effects on human health and well-being out of all the pharmaceuticals that might legitimately claim the moniker "Wonder drug." Ivermectin, however, can also be ranked with those deserving candidates because to its adaptability, safety, and positive effects that it has had and is still having on millions of the world's poorest people.

Ivermectin is still a relatively unknown drug today, despite the fact that few, if any, other medications can compare to it in terms of their positive effects on human health and welfare. Ivermectin is a broad-spectrum anti-parasitic drug that is mostly used in veterinary and human medicine to treat parasitic worms. This novel substance is effective against numerous parasite-induced epidermal parasitic skin disorders, insect infestations, and other worm-related infections and diseases. It has mostly been used in humans as an oral drug to treat filarial diseases. It is supposedly used to treat Onchocerciasis,lymphatic, filariasis, strongyloidiasis, scabies, and, most recently, head lice. It is approved for human usage in a number of countries.(2)

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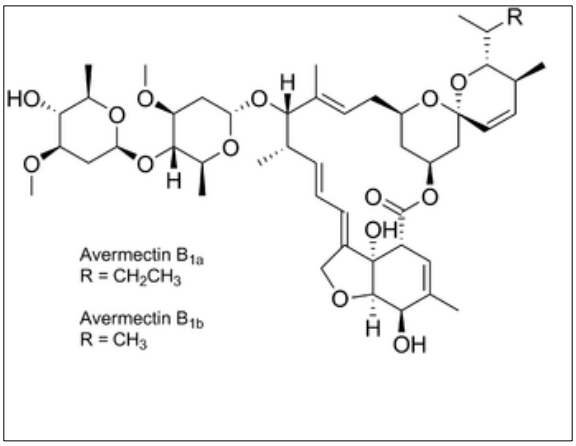

What You Should Know About Ivermectin is Provided Below

- Ivermectin has not been authorized or approved by the FDA for use in either human or animal COVID-19 prevention or treatment. Humans can use ivermectin to treat illnesses brought on by parasitic worms, head lice, and skin problems like rosacea.
- Data at this time do not support ivermectin's COVID-19 efficacy. Ivermectin pills are currently the subject of clinical research evaluating their efficacy in human COVID-19 prevention or treatment.
- Ivermectin should never be taken in high amounts. If your doctor gives you a prescription for ivermectin, fill it at a reputable location, like a drugstore, and take it exactly as directed.

2. Ivermectin

2.1. What Is It and How Is It Used?

The FDA has approved ivermectin pills for the treatment of intestinal strongyloidiasis and onchocerciasis, two illnesses brought on by parasitic worms. Additionally, some topical applications of ivermectin are authorized for the treatment of skin diseases including rosacea as well as external parasites like head lice. Heartworm disease prevention and the treatment of some internal and external parasites are both permitted uses for some types of animal ivermectin. It's significant to note that these products are unique from those intended for humans and are only safe when administered to animals in accordance with directions.

2.2. Ivermectin against bacteria

Ivermectin has a strong antibacterial impact, making it the best medication for those with compromised immune systems. Additionally, it stops them from procreating. Additionally, it helps those who experience allergic reactions. Only those who experience mild or allergic responses after taking other anti-infested medications are affected by it.

The only medication that has been approved to treat this reaction is ivermectin. Ivermectin works in a way similar to antibiotics. It causes the bacterial cell to burst, which helps to kill antibiotic-resistant bacteria.Ivermectin is more effective in treating germs that have evolved over many generations than antibiotics.

Ivermectin inhibits the bacterial protease (lysine protease) and the permeability of the bacterialmembrane to produce antimicrobial actions against the bacteria *Vibrio cholera*. These bacterial peptidases are constrained by the peptidyl transfer protein LYPR1. Ivermectin also inhibits the activity of proteinases and the permeability of bacterial membranes. Additionally discovered to have anti-biofilm action is ivermectin.

2.3. Creating ivermectin for human consumption

Early research by Merck's William Campbell and his team revealed that the medication also combated a human parasite that causes the infection known as river blindness.

Onchocerciasis, sometimes referred to as river blindness, is the second-leading global cause of avoidable blindness. It mostly occurs in Africa and is spread to people by blackfliesthat have the parasite worm volvulus.

In 1982, ivermectin underwent river blindness studies; it was authorized in 1987. Since then, dozens of nations have received it for free through the Donation Program. Ivermectin has essentially eradicated river blindness in 11 countries in Latin America, averting 600,000 cases of blindinfectious disease researchers frequently attempt to repurpose antimicrobials and other medications to treat infections.Drug repurposing is appealing because, since almost all of the basic research has already been conducted, the approval procedure can go more swiftly and for less money.

Ivermectin has proven to be quite successful against various parasite illnesses in the years after it was authorized to treat river blindness. Included in this is strongyloidiasis,a roundworm infection of the intestine that affects between 30 and 100 million individuals globally.

2.4. WHO advises that ivermectin only be used to treat COVID-19

Ivermectin may be used to treat COVID-19 patients, although the available research is inconsistent. WHO recommends that the medicine only be used in clinical trials up until more information is known.

This recommendation, which applies to patients with COVID-19 of any disease severity, is now part of WHO's guidelines on COVID-19 treatment.

In response to the rising international interest in ivermectin as a potential COVID-19 treatment, a guideline development group was established. A clinical care specialist from each specialty is represented on an independent, multinational panel of experts, along with an ethicist and patient partners.

The team looked at combined data from 16 randomized controlled studies (total participants: 2407), which included patients with COVID-19 who were both inpatients and outpatients. Due to the small sizes and methodological restrictions of the available trial data, including the small number of events, they concluded that the evidence on whether ivermectin reduces mortality, the need for mechanical ventilation, the need for hospital admission, and the time to clinical improvement in COVID-19 patients is of "very low certainty."

2.5. Ivermectin against COVID-19

Ivermectin reportedly inhibits host importin alpha/beta-1 nuclear transport proteins, which are a crucial component of intracellular transport. Viruses hijack the process and promote infection by blocking the host's antiviral response. Additionally, docking of ivermectin may prevent SARS-CoV-2 spike protein from attaching to the human cell membrane, according to certain studies. COVID-19 patients may benefit from these putative anti-inflammatory properties.

Ivermectin has been studied in observational and randomized studies since the SARS-CoV-2 pandemic began to spread as a therapy and prevention against COVID-19 infection. Ivermectin "demonstrates a high signal of therapeutic activity" against COVID-19, according to a review of the Front Line COVID-19 Critical Care Alliance that compiled data from research on its impact for the prevention and treatment of COVID-19 infection. Ivermectin was reported to have a 75% reduction in fatalities in another recent analysis.Despite these results, the World Health Organization advises against using ivermectin outside of clinical trials, and the National Institutes of Health in the United States recently stated that "there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19."

Several DNA and RNA viruses, including Zika, dengue, yellow fever, and others, have been shown to be resistant toivermectin's antiviral effects. With a host-directed mode of action that is considered to be the inhibition of viral proteins' nuclear import, which suppresses natural immune responses, Calyet. demonstrated specific action against SARS-CoV-2 *in vitro*. The required cell culture EC50, though, might not be possible *in vivo*. Ivermectin's competitive interaction with the viral S protein, as demonstrated by numerous in silico studies, and inhibition of SARS-CoV-2 3CLPro activity (a protease required for viral replication) are further hypothesized causes.In the latter, viral attachment to ACE-2 receptors would be inhibited, so preventing infection.(5)

2.6. Rationale

Ivermectin use in patients with COVID-19 has been the subject of numerous randomized trials and retrospective cohort studies, the findings of which;

The objective of this evaluation was to evaluate the effectiveness of ivermectin treatment for those who had COVID-19 infection as well as for those who were at higher risk of getting COVID-19 infection. Additionally, we wanted to write a short economic commentary (BEC) on the use of ivermectin for COVID-19 prevention and treatment.

Comparedto the combination of hydroxychloroquine and azithromycin, ivermectin is more affordable. It is a more attractive choice for clinical trials because of its overall cost-effectiveness and safety profile. Ivermectin is not advised for these population groups since there is inadequate data to support its safety at larger doses in children under 15 kg and pregnant women [12]. A herd mentality still prevails in India due to widespread disease fear, and questions about drug dosages and how to take them are still frequently asked on social media [13]. Ivermectin experienced a rapid increase in over-the-counter sales in a short period of time after word spread on social media that the ICMR had included the drug in its COVID-19 treatment guidelines.

3. Main Termination

3406 participants were enrolled in 24 RCTs (including 3 quasi-RCTs), with sample sizes ranging from 24 to 476 participants. Three prophylaxis trials and 22 treatment trials. The trial reported both components, satisfying review inclusion criteria. Six trials included patients with severe COVID-19, and 16 trials for COVID-19 treatment exclusively examined ivermectin among participants with mild to moderate COVID-19. Three trials contained an active comparator; the majority compared ivermectin with a placebo or no ivermectin. Most compared ivermectin with placebo or no ivermectin; 3 trials included an active comparator. Three RCTs involving 738 participants were included in the prophylaxis trials. Most trials were registered, self-funded, and undertaken by clinicians working in the field. There were no obvious conflicts of interest noted, with the exception of two trials.

Twenty-one COVID-19 treatment trials and two COVID-19 prophylactic trials fulfilled the review inclusion criteria. One further study47, which we refer to as"Elgazzar" for both issues, provided independent treatment and prophylactic components. In actuality, there were 3 prophylactic trials and 22 therapy trials. Each of them provided information for at least one meta-analysis and review result. Three studies reported the primary outcome for prophylaxis, and fifteen trials provided data for the treatment's main endpoint (death) (COVID-19 infection). Table Table1.1 lists the characteristics of the studies that were included. We found 39 continuing studies64-102, 17 studies47-63 that were omitted because they were not RCTs, and 2 studies103, 104 that are still awaiting classification.

Finally, 16 people received ivermectin (150 g/kg) together with water or orange juice (750 ml). AUC (15.7 ng d ml) and C max (20.7 ng ml) of orange juice were lower than those of water (33.8 ng ml and 24.3 ng ml, respectively), possibly because fruit juices and their contents are strong inhibitors of several drug transporters (20).

Table 1 Summary of study characteristics

Study ID	Country	Design	Funding	Participants	Sample size	Ivermectin dose and frequency*	Comparator	Origin of data	Main outcomes reported
COVID-19 treatment studies									
Ahmed 2020[23]	Bangladesh	Double-blind	BPL(Pharma); Bangladesh, Canada, Sweden, and UK govt	Mild to moderate COVID (inpatients)	72	12 mg × 1 day or × 5 days (3 study arms)*	Placebo	Published in PR journal; emailed/responded with data	Time to viral clearance (PCR –ve), remission of fever and cough within 7 days, duration of hospitalization, mortality, failing to maintain sats>93%, adverse events, PCR –ve at 7 and 14 days
Babalola 2020[105]	Nigeria	Double-blind	Self-funded	Asymptomatic, mild or moderate COVID (45 inpatients and 17 outpatients)	62	6 mg every 84 hrs × 2 wks (arm 1) or 12 mg every 84 hrs × 2 wks (arm 2)	Ritonavir/lopinavir	MedRxiv preprint: emailed/responded with data. Paper accepted for publication	Time to PCR –ve, laboratory parameters (platelets, lymphocytes, clotting time), clinical symptom parameters
Bukhari 2021[135]	Pakistan	Open-label	None reported	Mild to moderate COVID (inpatients)	100	12 mg × 1 dose	SOC	MedRxiv preprint	Viral clearance, any adverse side effects, mechanical ventilation
Chaccour 2020[24]	Spain	Double-blind	Idapharma, ISGlobal, and the University of Navarra	Mild COVID (outpatients)	24	0.4 mg/kg × 1 dose	Placebo	Published in PR journal	PCR +ve at day 7, proportion symptomatic at day 4,7,14,21, progression, death, adverse events

Chachar 2020[112]	Pakistan	Open-label	Self-funded	Mild COVID (outpatients)	50	12 mg at 0, 12, and 24 hours (3 doses)	SOC	Published in PR journal	Symptomatic at day 7
Chowdhury 2020[136]	Bangladesh	Quasi-RCT	None reported	Outpatients with a +ve PCR (approx. 78% symptomatic)	116	0.2 mg/kg x1 dose*	HCQ 400 mg 1st day then 200 mg BID × 9 days + AZM 500 mg daily × 5 days	Research square preprint	Time to –ve PCR test; period to symptomatic recovery; adverse events
Elgazzar 2020[47]	Egypt	RCT	None reported	Mild to severe COVID (inpatients)	200	0.4 mg/kg daily × 4 days	HCQ 400 mg BID × 1 day then 200 mg BID × 9 days	Research square preprint: emailed/responded with data	Improved, progressed, died. Also measured CRP, D-dimers, HB, lymphocyte, serum ferritin after one week of treatment
Fonseca 2021[44]	Brazil	Double-blind	Institution-funded	Moderate to severe (inpatients)	167	14 mg daily × 3 days (plus placebos × 2 additional days)	HCQ—400 mg BID on day 0 then daily × 4 days; CQ -450 mg BID day 0 then daily × 4 days	Prepublication data/manuscript in progress obtained via email	Death, invasive mechanical ventilation
Gonzalez 2021[137]	Mexico	Double-blind	Institution-funded	Moderate to severe (inpatients)	108	12 mg × 1 dose	Placebo	MedRxiv preprint	Length of hospital stay, invasive mechanical ventilation, death, time to negative PCR
Hashim 2020[138]	Iran	Quasi-RCT	None reported	Mild to critical (inpatients)	140	0.2 mg/kg × 2 days* Some had a 3rd dose a week later	SOC	MedRxiv preprint	Death, mean time to recovery, disease progression (deterioration)
Krolewiecki 2020[106]	Argentina	Open-label	None reported	Mild to moderate (inpatients)	45	0.6 mg/kg/d × 5 days	Placebo	Research Gate and SSRN preprints	Viral load reduction in respiratory secretions day 5, IVM concentrations in plasma, severe adverse events

Lopez-Medina 2021[85]	Columbia	Double-blind	Institution-funded	Mild (outpatients)	476	0.3 mg/kg elixir × 5 days	Placebo	Published in a PR journal	Resolution of symptoms within 21 days, deterioration, clinical condition, hospitalization, adverse events
Mahmud 2020[107]	Bangladesh	Double-blind	None reported	Mild to moderate COVID (inpatients)	363	12 mg × 1 dose*	Placebo + SOC	Data published on clinical trial registry and clarification obtained via email	Improvement, deterioration, late clinical recovery, persistent PCR test +ve
Mohan 2021[110]	India	Double-blind	Institution-funded	Mild to moderate	152	12 mg or 24 mg elixir × 1 dose	Placebo	MedRxiv preprint research	Conversion of RT-PCR to negative result, decline of viral load at day 5 from enrollment
Niaee 2020[108]	Iran	Double-blind	Institution-funded	Mild to severe COVID	180	0.2 mg/kg × 1 and 3 other dosing options) ~ 14 mg tablet†	Placebo	Research Square preprint	Deaths, length of stay, biochemical parameters
Okumus 2021[115]	Turkey	Quasi-RCT	None reported	Severe COVID	66	0.2 mg/kg × 5 days	SOC	Prepublication data/manuscript in progress obtained via email	Clinical improvement, deterioration, death, SOFA scores
Petkov 2021[139]	Bulgaria	Double-blind	Pharma-funded	Mild to moderate COVID	100	0.4 mg/kg × 3 days	Placebo	Prepublication data obtained from another source	Rate of conversion to PCR negative
Podder 2020[140]	Bangladesh	Open-label	Self-funded	Mild to moderate (outpatients)	62	0.2 mg/kg × 1 dose	SOC	Published in PR journal	Duration of symptoms, recovery time to symptom free from enrollment, recovery time to symptom free from symptom onset,

									repeat PCR result on day 10
Raad 2021[113]	Lebanon	Double-blind	Self-funded	Asymptomatic outpatients	100	9 mg PO if 45 kg–64 kg, 12 mg PO if 65 kg–84 kg and 0.15 mg/kg if body weight ≥85 kg	Placebo	Prepublication data/manuscript in progress obtained via email	Viral load reduction, hospitalization, adverse effects
Ravikirti 2021[109]	India	Double-blind	Self-funded	Mild to moderate COVID (inpatients)	112	12 mg × 2 days + SOC	Placebo + SOC	Published in PR journal	A negative RT-PCR report on day 6, symptomatic on day 6, discharge by day 10, admission to ICU, need for invasive mechanical ventilation, mortality
Rezai 2020[111]	Iran	Double-blind	None reported	Mild to moderate (inpatient)	60	0.2 mg/kg × 1 dose	SOC	Prepublication data obtained from another source	Clinical symptoms, respiratory rate and O2 saturation
Schwartz 2021[114,141]	Israel	Double-blind	None reported	Mild to moderate (outpatients)	94	0.15–0.3 mg/kg × 3 days	Placebo	Prepublication data obtained from another source	Viral clearance at day 4, 6, 8 and 10), hospitalization
COVID-19 prophylaxis studies									
Chahla 2021[142]	Argentina	Open-label	None reported	Health care workers	234	12 mg (in drops) weekly + iota-carrageenan 6 sprays daily × 4 wk	SOC	Prepublication data/manuscript in progress obtained via email	COVID-19 infection (not clear if measured by PCR or symptoms)
Elgazzar 2020[47]	Egypt	Open-label	Self-funded	Health care and family contacts	200	0.4 mg/kg, weekly × 2 weeks	SOC	Research square preprint:	Positive PCR test

								emailed/responded with data	
Shouman 2020[143]	Egypt	Open-label	Self-funded	Family contacts	304	2 doses (15–24 mg depending on weight) on day 1 and day 3	SOC	Published in PR journal	Symptoms and/or positive COVID-19 PCR test within 14 days; adverse events

3.1. Drug-Drug Interactions, Monitoring, and Adverse Reactions

- Ivermectin side effects can includepruritisand dizziness.
- Ivermectin has been used to treat parasitic diseases like onchocerciasis, but there have been reports of neurological side effects as well. It is unclear whether these side effects were brought on by the drug itself or by the underlying conditions.
- Ivermectin is a p-glycoprotein substrate and a minor cytochrome P450 3A4 substrate.
- Ivermectin is typically administered with water on an empty stomach, however, doing so increases the drug's bioavailability.

3.2. Effects of early treatment with ivermectin among the patients of COVID-19

Overall (2157). In all, 100 patients (14.7%) in the ivermectin group and 111 (16.3%) in the placebo group experienced a primary outcome event (relative risk, 0.90; 95% Bayesian credible interval, 0.70 to 1.16). Hospital admissions made up 171 (81.0%) of the 211 primary-outcome occurrences. A modified intention-to-treat analysis that only included patients who received at least one dose of ivermectin or placebo and a per-protocol analysis that only included patients who reported 100% adherence to the prescribed regimen both produced similar results to the primary analysis (relative risk, 0.89; 95% Bayesian credible interval, 0.69 to 1.15; and relative risk, 0.94; 95% Bayesian credible interval, 0.67 to 1.35).(4)

3.3. Immune System Effects of Ivermectin

Ivermectin's immunomodulation of the host is one of its primary pharmacodynamic effects [7,8]. It controls animal glucose and cholesterol levels and prevents the growth of cancer cells [9]. In addition to being molecules with antibacterial activity, macrolide antibiotics are helpful in the treatment of a few inflammatory illnesses [10,11,12]. Ivermectin is a semi-synthetic macrocyclic lactone that, like other macrolides, inhibits the release of prostaglandin E2 and NO when lipopolysaccharide (LPS) is present [13,14]. The LPS-induced mortality in mice is most effectively inhibited at a dose of 2 mg/kg. The generation of TNF-a, IL-1b, and IL-6 was also seen to be inhibited. Experiments carried out *in vitro* using RAW 264.

3.4. When is it unsafe to take ivermectin?

Ivermectin has not been given FDA approval or authorization to treat or prevent COVID-19 in humans or animals. For these indications, ivermectin's safety or efficacy has not been established.

There is a lot of false information out there, and you might have heard that taking high doses of ivermectin is acceptable. It's unacceptable.

Even ivermectin at levels deemed safe for use in humans can interact with other drugs, such as blood thinners. Ivermectin overdose can result in nausea, vomiting, diarrhea, low blood pressure, allergic responses (itching and hives), dizziness, ataxia (balance issues), seizures, coma, and even death.

3.5. Brand names

Table 2 Different brands of ivermectin

S.No	Brands
1	Heart gard
2	sklice
3	Stromectol
4	Ivomec
5	Mectizan
6	Ivexterm
7	Iver-DT
8	Scabo 6
9	MK-933

4. Conclusion

Significant progress has been achieved in the last ten years in the creation of repurposed medications for the treatment of bacterial and viral infections. Several drugs have produced encouraging results, but preclinical research is still being done. In the preclinical development of repurposing drugs, additionalpertinent factors should be taken into consideration, such as the potential need for new formulations to increase their bioavailability and ADMET tests if the route of administration is changed, the potential for adverse effects on the primary drug activity (especially for anticancer and antipsychotic drugs), and difficulties with intellectual property rights. Additionally, more clinical research is required to meet the pressing need for fresh therapies that target bacterial and viral diseases.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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